Factors affecting coagulation: fibrinolysis in chronic subdural fluid collections

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Plasminogen, alpha2-antiplasmin, fibrinogen, fibrin degradation products (FDP's), and hemoglobin were measured in the supernatant fluid of 25 chronic subdural hematomas and five chronic subdural hygromas. The 30 patients underwent pre- and postoperative computerized tomography. The hematomas were characterized by low fibrinogen and high fibrin degradation product concentrations. The hemoglobin content varied directly with the alpha2-antiplasmin, and inversely with the plasminogen. Four patients underwent reoperation for recurrences. The initial fluid from these cases was characterized by relatively high plasminogen and low alpha2-antiplasmin. The hygromas had no hemoglobin, and low fibrinogen, high FDP's, low alpha2-antiplasmin, and variable plasminogen levels. It is possible that those cases having the greatest capacity to produce plasmin (high plasminogen and low alpha2-antiplasmin) can produce more FDP's which in turn causes more rebleeding and an increased risk of reaccumulation of chronic subdural hematomas.

KEY WORDS · chronic subdural hematoma · subdural hygroma · hemoglobin · plasminogen · fibrinogen · fibrin degradation product · antiplasmin

MORE than 150 years ago, Bayle suggested that chronic rebleeding caused growth of subdural hematomas.9 The following observations concerning chronic subdural hematomas have been widely recognized over much of the intervening time.12 Such hematomas contain fresh erythrocytes despite the duration of symptoms. Their contents do not clot on standing, and can inhibit normal blood clotting. Chronic hematomas occur frequently in patients with acquired bleeding disorders. The hematomas may be cured by a single removal of fluid via a burr hole, which leaves most of the vascular outer membrane intact and in situ. There is a progressive diminution in the erythrocyte count and hemoglobin content of residual subdural fluid following the initial drainage. Acute and subacute hematomas may be found in layers on the dural side of a chronic hematoma. Despite these common clinical observations, the paramount importance of defective local hemostasis and chronic rebleeding in the late growth of chronic subdural hematomas has only been accepted recently.

We thought it worthwhile to study the factors in chronic subdural fluid collections that are of potential significance for clot production and breakdown.

Materials and Methods

Subdural fluid from 30 patients with chronic collections was aspirated through the dura with a sharp needle via a burr hole. Care was taken to avoid contamination by extraneous blood. Patients had pre- and postoperative computerized tomography (CT) scans. Twenty-five had hematomas. Four patients with hematomas subsequently underwent reoperation for persistent symptomatic collections.

Samples were transported to the laboratory and centrifuged at 1600 G for 10 minutes. The supernatant was immediately stored at -70°C until analysis.

Hemoglobin was measured by means of a Coulter counter,* based on the principle of conversion to cyanmethemoglobin. Fibrinogen was measured with a Dade fibrinogen determination test kit,† which uses a method based on clotting in the presence of excess thrombin2 (normal adult plasma fibrinogen: 190 to 400 mg/dL).

* Coulter counter, Model S, manufactured by Coulter Electronics Inc., Hialeah, Florida.
† Dade fibrinogen determination test kit, supplied by Dade Division, American Hospital Supply Corp., Miami, Florida.
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![Graph showing hemoglobin, plasminogen, and alpha2-antiplasmin levels in hematoma and hygroma](Image)

FIG. 1. Results from measurement of several parameters in 25 chronic hematomas and five hygromas. The values for all three factors in any one case are aligned vertically. They are illustrated in order of decreasing hemoglobin concentrations. The “R”'s indicate the four hematoma patients who underwent reoperation for recurrent collections.

450 mg/100 ml). Fibrin degradation products (FDP’s) were assayed using the Thrombo-Welcotest latex slide test‡ (normal plasma level: < 10 µg/ml). Plasminogen and alpha2-antiplasmin levels were estimated by fluorescent substrate assays§. Normal adult plasminogen activity in plasma is 3.1 ± 0.7 CTA (Committee on Thrombolytic Agents) units/ml, and normal adult range for alpha2-antiplasmin is 80% to 120% of normal control plasma.

Results

Concentrations of hemoglobin, plasminogen, and alpha2-antiplasmin are shown in Fig. 1. There was a tendency for the hemoglobin concentration to vary directly with the alpha2-antiplasmin, and inversely with the plasminogen in the chronic subdural hematomas.

Hemoglobin

The hemoglobin content of the supernatant of the 25 chronic hematoma fluids was 3.1 ± 0.6 gm/dl. One of the five fluids classified as a hygroma (because the collection was hypodense on CT scan) had no membranes and was grossly clear. This sample was found to have 0.2 gm/dl of hemoglobin; the remainder of the hygromas had none.

Fibrinogen

No fibrinogen was detected in any samples. However, the method is of limited accuracy when fibrinogen concentrations are less than 15 mg%.

Fibrin Degradation Products

All specimens from hematomas contained FDP’s of more than 40 µg/dl. Four of the five hygromas also had FDP’s over 40 µg/dl, although one of them had a concentration of less than 10 µg/dl.

Plasminogen

The mean concentration of plasminogen was 0.63 ± 0.62 CTA units/ml, with a range of 0 to 2 CTA units/ml in the 25 hematomas. For hygromas, the mean was 0.62 ± 0.52 CTA units/ml and the range was 0 to 1.2 CTA units/ml.

Alpha2-Antiplasmin

For 25 hematomas, the mean alpha2-antiplasmin activity was 108 ± 56% (range 0 to 200%). The mean activity for five hygromas was 22 ± 18% (range 0 to 38%).

The width of the hematoma postoperatively, and the hemoglobin, plasminogen, and antiplasmin levels in reoperated and non-reoperated cases are compared

‡ Thrombo-Welcotest latex slide test supplied by Wellcome Reagents Ltd., Beckenham, England.
§ Protopath fluorometer manufactured by Dade Division, American Hospital Supply Corp., Miami, Florida.
TABLE 1

Summary of findings in 30 patients with chronic subdural fluid collections*

<table>
<thead>
<tr>
<th>Diagnosis &amp; No. of Ops</th>
<th>No. of Cases</th>
<th>Width of Collection†</th>
<th>Hemoglobin (gm/dl)</th>
<th>Plasminogen (CTAU/ml)</th>
<th>Alpha2-Antiplasmin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hematoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one op</td>
<td>21</td>
<td>26 ± 4</td>
<td>3.5 ± 0.8</td>
<td>1.1 ± 0.5</td>
<td>118 ± 12</td>
</tr>
<tr>
<td>two ops</td>
<td>4</td>
<td>99 ± 18</td>
<td>0.8 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td>53 ± 21</td>
</tr>
<tr>
<td>hygroma, one op</td>
<td>5</td>
<td>62 ± 17</td>
<td>0.04 ± 0.03</td>
<td>0.7 ± 0.3</td>
<td>22 ± 9</td>
</tr>
</tbody>
</table>

* Figures are means ± SEM. T-tests showed significant differences between the cases having a single operation and those requiring reoperation in postoperative width, alpha2-antiplasmin, hemoglobin (p < 0.05), and plasminogen (p < 0.01). The single-operation hematoma cases differed significantly from the hygroma cases in alpha2-antiplasmin (p < 0.01) and hemoglobin (p < 0.001). CTAU = Committee on Thrombolytic Agents units.

† Percentage reduction seen on postoperative computerized tomography scans compared with preoperative studies.

Fig. 2. Simplified schema for fibrinolysis, showing changes in chronic hematoma fluid compared to blood. FDP = fibrin degradation products; Hgb = hemoglobin.

Discussion

Although the coagulation process usually occurs rapidly following blood vessel damage, fibrinolysis is slower, but is a continuous process beginning almost as soon as a clot is formed. The neocapillary bed from the dura, which is the external membrane of the chronic subdural hematoma, appears from electron microscopy studies to be abundant in blood vessels. Vascular permeability is increased, and bleeding occurs easily from these capillaries, especially in the presence of degenerative endothelial cells. Ito, et al., using erythrocytes labeled with chromium-51, showed evidence of ongoing daily hemorrhage in five patients with subdural hematomas, and indicated that in cases with bilateral hematomas, the amount of hemorrhage was greatest on the side with the higher level of FDP's.

Subsequent studies have shown high plasminogen activator levels in the vascular outer membrane (consistent with the evidence that an important source of plasminogen activator is vascular endothelium), and that plasminogen and available plasmin is extremely low in hematomas which also contain elevated FDP's. This suggested enhanced fibrinolytic activity, which might then be associated with further bleeding. Fibrin degradation products are well known to have an anticoagulant effect, but they may also inhibit platelet aggregation and produce a vasodilator effect.11

The results of this study show findings similar to those of Ito, et al., as seen in the schema illustrated in Fig. 2. However, we also measured alpha2-antiplasmin, since it has only recently been recognized that this protein is physiologically the most important plasmin inhibitor in plasma. Rare patients with a hemorrhagic diathesis due to deficiency in alpha2-antiplasmin have been described. The inverse relationship between plasminogen and alpha2-antiplasmin is intriguing, particularly so since we found that patients who needed reoperation tended to have the highest plasminogen and lowest antiplasmin levels. Perhaps these cases were able to produce the highest plasmin levels, resulting in further production of FDP's and greater tendency to rebleeding. This suggests that further studies are warranted, including serial measurements of plasmin and alpha2-antiplasmin complexes as an index of ongoing fibrinolytic activation in vivo, since it raises the possibility of assays of chronic subdural fluid being helpful in predicting which patients might be at greater risk from reaccumulation of hematoma. In such cases, longer periods of external drainage might be indicated and/or the use of fibrinolytic inhibitor drugs.

References

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