Coagulation Abnormalities in Subarachnoid Hemorrhage

BY M. G. ETTINGER, M.D.*

Abstract:
Coagulation and fibrinolytic studies were performed in 30 subarachnoid hemorrhage patients and 30 age-matched and sex-matched controls.
Systemic abnormalities were detected in the following tests: recalcification time, fibrinogen, partial thromboplastin time, K value of thromboelastogram and euglobulin lysis time.
The data suggest that subarachnoid hemorrhage patients with fibrinogen values over 400 mg% have a low probability of survival.
Test abnormalities probably reflect tissue damage and/or meningeal reaction to the subarachnoid hemorrhage. Similar abnormalities can be noted in patients with cerebral trauma and in some patients with nonhemorrhagic cerebrovascular disease.¹
Our data reveal that subarachnoid hemorrhage patients may exhibit simultaneously evidence suggesting increased coagulability and activation of fibrinolytic mechanisms. Under these circumstances administration of agents to suppress lytic activity might lead to disastrous consequences such as widespread intervascular coagulation (consumption coagulopathy).

ADDITIONAL KEY WORDS fibrinolysis fibrinogen E-aminocaproic acid intracranial aneurysms

Introduction
□ This report describes changes in coagulation and fibrinolytic mechanisms which may accompany subarachnoid hemorrhage. The specific study objectives were to seek answers to the following questions: (1) Are systemic clotting abnormalities detectable following subarachnoid hemorrhage? (2) If so, do they have any prognostic implications regarding gross mortality or rebleeding episodes from aneurysms? (3) If any of the above correlations are positive, can the clotting abnormalities themselves be responsible for an undesirable result, or do they simply accompany such results? (4) If the clotting abnormalities contribute in some way to an undesirable result, can they be altered to effect a better result? This report attempts to answer the first and possibly the second questions posed above in the affirmative.

Method
A coagulation test battery† was utilized in the

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†Details concerning the methods of the battery of coagulation tests will be supplied by the author upon request.
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FIGURE 1

Tests revealing no significant differences between patients and controls.

- Prothrombin time
- Platelets
- Antithrombin
- Thromboplastin generation time (1/50)
- Thrombin time
- Thromboelastogram—R
- Thromboelastogram—MA
- Factor II
- Factor V
- Factor VIII

Investigation of 30 subarachnoid hemorrhage patients and 30 controls. The subarachnoid hemorrhage patients were consecutive admissions to the Hennepin County General Hospital with a diagnosis of nontraumatic subarachnoid hemorrhage confirmed by lumbar puncture. The controls were age-matched and sex-matched healthy volunteers from the hospital and surrounding community. All tests were performed in a fasting state, and blood was drawn at 8:00 A.M. for all studies.

The coagulation test battery consisted of the following: prothrombin time; platelet count; recalcification time; fibrinogen; antithrombin; partial thromboplastin time; thromboplastin generation tests (1:50 dilution); thromboelastogram; thrombin time; euglobulin lysis time, and assay of factors II, V and VIII. The coagulation studies were performed within 48 hours of the bleeding episode in all patients. Daily studies were performed in a few patients.

**Results**

The following tests in subarachnoid hemorrhage patients did not differ significantly from the controls: prothrombin time, platelets, antithrombin, thromboplastin generation time, thrombin time, thromboelastogram values R and MA, assay of factors II, V and VIII (fig. 1).

Test values revealing significant differences between subarachnoid patients and controls included recalcification time, fibrinogen, partial thromboplastin time, thromboelastogram value K, and euglobulin lysis time (fig. 2 and table 1). The abnormalities in recalcification, fibrinogen, PTT and TEG-K are all consistent with the hypothesis that these patients are demonstrating increased coagulability in their systemic venous blood within 48 hours following a subarachnoid hemorrhage. At the same time, variation in euglobulin lysis studies demonstrates that these patients also have increased fibrinolytic activity. Our data suggest, therefore, that increased coagulation and increased lysis are occurring simultaneously in patients following subarachnoid hemorrhage, and we have to date found only 2 patients of the 30 who exhibited a change in one area, such as increased coagulation, and not in the other.

Investigating the possible relationship between the test abnormalities and gross mortality, we find such a correlation only with fibrinogen values (table 2). Considering patients with fibrinogen values above 400 mg%, there was an 87% mortality rate (seven out of eight); those with fibrinogen values below 400 mg% demonstrated a mortality rate of 36%. It should be noted, however, that of the total number of patients who died (15) slightly less than 50% (seven) were noted to have fibrinogen values exceeding 400 mg%.

An attempt was made to assess the

**TABLE 1**

Tests Revealing Significant Differences Between Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th></th>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
<th>Significant values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Mean</td>
<td>S.E.</td>
<td>Number</td>
<td>Mean</td>
<td>S.E.</td>
<td>T tests</td>
</tr>
<tr>
<td>Recalcification</td>
<td>30</td>
<td>99</td>
<td>4.5</td>
<td>30</td>
<td>108</td>
<td>3.0</td>
<td>.078</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>30</td>
<td>324</td>
<td>24.0</td>
<td>30</td>
<td>280</td>
<td>12.0</td>
<td>.036</td>
</tr>
<tr>
<td>PTT (Pt./Control)</td>
<td>30</td>
<td>88</td>
<td>2.0</td>
<td>30</td>
<td>102</td>
<td>2.5</td>
<td>.036</td>
</tr>
<tr>
<td>TEG-K</td>
<td>30</td>
<td>6</td>
<td>0.4</td>
<td>30</td>
<td>11</td>
<td>0.8</td>
<td>.001</td>
</tr>
<tr>
<td>Lysis (at 4 hrs.)</td>
<td>30</td>
<td></td>
<td></td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight to moderate</td>
<td>93%</td>
<td>50%</td>
<td></td>
<td>50%</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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COAGULATION ABNORMALITIES

TABLE 2

<table>
<thead>
<tr>
<th>Relationship Between Fibrinogen Values and Mortality Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Survived</td>
</tr>
<tr>
<td>Died</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Mortality Rate: <400 = 36%
>400 = 87%

possible significance of these abnormalities in relation to the problem of rebleeding from ruptured aneurysm. We were fortunate in having an opportunity to obtain the coagulation test battery 24 hours or less preceding a rebleeding episode in three patients who were initially hospitalized with a diagnosis of subarachnoid hemorrhage secondary to ruptured aneurysm (table 3). In two of the three patients we were able to secure euglobulin lysis studies less than 24 hours preceding, and within 24 hours following, the rebleeding episode. In the third patient we obtained values before the rebleed, but not subsequently. It should be noted that although our study generally suggests an increased incidence of fibrinolytic activity following subarachnoid hemorrhage, in none of these three patients was there an increase in fibrinolytic activity preceding the rebleeding episode, and in two out of three there was no increased activity following the rebleed. We have, therefore, no direct evidence that fibrinolytic activity contributes to rebleeding from ruptured aneurysm.

Discussion

A number of reports have appeared in the recent literature concerning the effect of cerebrospinal fluid on systemic coagulation mechanisms. De Vivo, Kline and Dodge were concerned with the possible adverse effect of shunting cerebrospinal fluid into the vascular system in hydrocephalic patients. They demonstrated significant acceleration of clot formation using thrombin and thromboplastin test systems. This effect was noted in from 76% to 83% of cerebrospinal fluid samples tested. They also demonstrated evidence for the presence of an inhibitory factor in normal cerebrospinal fluid when utilizing various prothrombin test systems. Niewiarowski et al. concluded that factor V activity is present in cerebrospinal fluid. They also noted a trace of prothrombin activity and negligible factor VII and VIII activity in their cerebrospinal fluid samples. Wilkins et al. explored the possibility that cerebrospinal fluid may influence the recurrent hemorrhage rate in intracranial aneurysm. In 50 normal cerebrospinal fluid samples no thrombin, fibrinogen, prothrombin, proconvertin, proaccelerin, factor VIII, or thromboplastic activity was found. They concluded that cerebrospinal fluid did not interfere with or in any way influence the healing of ruptured aneurysm.

Very few investigations into cerebrospinal fluid fibrinolytic activity have been reported. Roberts and Astrup, in 1957, and Moltke in 1958 demonstrated fibrinolytic activity in dura and pia of various animal species. In 1958 Albrechtsen, Storm, and Classen found an incomplete activator of fibrinolytic activity in human cerebrospinal fluid. Porter et al. in 1969 confirmed the above results in humans and further investigated the ability of systemically administered fibrinolysin and E-aminocaproic acid (Amicar) to penetrate into the cerebrospinal fluid. Thrombolysin did not appear to penetrate the blood-brain barrier in animals, whereas aminocaproic acid did seem to alter the cerebrospinal fluid fibrinolytic activity in seven of the ten animals studied.

In view of the current interest in using E-aminocaproic acid to prevent rebleeding in patients with subarachnoid hemorrhage, this study was undertaken to assess coagulation and fibrinolytic abnormalities in patients with

TABLE 3

<table>
<thead>
<tr>
<th>Euglobulin Lysis Values Preceding (24 Hours) Rebleeding Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between 1st and 2nd bleed</td>
</tr>
<tr>
<td>B.D.</td>
</tr>
<tr>
<td>L.F.</td>
</tr>
<tr>
<td>R.G.</td>
</tr>
</tbody>
</table>
subarachnoid hemorrhage. Our data will be analyzed in the context of the questions posed in the introduction of this presentation as specific study objectives. (1) Are systemic clotting abnormalities detectable following subarachnoid hemorrhage? We have been able to identify abnormalities in at least five tests included in our coagulation test battery which appear to be frequently and significantly altered following subarachnoid hemorrhage. These tests are recalcification time, fibrinogen, partial thromboplastin time, the K value of thromboelastogram, and euglobulin lysis test.

(2) If so, do they have any prognostic implications regarding gross mortality and rebleeding from aneurysms? The only correlation made between gross mortality and the test values was noted in the fibrinogen determination. It was suggested that patients with fibrinogen values exceeding 400 mg% shortly after their bleeding episode had a very poor prognosis for survival. On the other hand, a low or normal fibrinogen was no guarantee of survival, as eight of the 22 patients with fibrinogen below 400 mg% also died. This gives us a mortality rate of 36% under 400 mg%, as compared with 87% above 400 mg%.

Regarding the second part of the question, "Is there any correlation between rebleeding from aneurysms and the tests performed," we were able to draw no positive correlations. However, in view of the current interest in the use of agents which inhibit fibrinolytic mechanisms as therapy to prevent rebleeding, there was no evidence of increased fibrinolytic activity.

These observations have direct implications regarding the use of aminocaproic acid or other fibrinolytic inhibitors for the treatment of subarachnoid hemorrhage in hopes of preventing rebleeding in such patients. The major hazard of such agents is that the lysis may be secondary to increased coagulation activity, and by administering effective doses the clotting abnormality proceeds unimpaired to result in widespread intravascular coagulation (consumption coagulopathy).

(3) If any of the above correlations are positive, can the clotting abnormalities themselves be responsible for an undesirable result, or do they simply come from such results? We have no evidence to suggest that these abnormalities precede or in any way cause subarachnoid hemorrhage. We feel that these changes most likely reflect tissue damage and/or meningeal reactions occurring following the acute episode.

(4) If these clotting abnormalities do contribute in some way to the undesirable result, can they be altered to effect a better result? We have insufficient data at the present time to arrive at any conclusions regarding the answer to this question. Further studies are contemplated.

Acknowledgment
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