Coagulation Abnormalities in Subarachnoid Hemorrhage

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

Abstract:
Coagulation abnormalities in 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.

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.
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

FIGURE 1

The 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
COAGULATION ABNORMALITIES

TABLE 2

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<th>Relationship Between Fibrinogen Values and Mortality Rates</th>
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<td></td>
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<tr>
<td>Survived</td>
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<tr>
<td>Died</td>
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<tr>
<td>Total</td>
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<td>Mortality Rate: 300 = 36%  &gt;400 = 87%</td>
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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. 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

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<th>Euglobulin Lysis Values Preceding (24 Hours) Rebleeding Episodes</th>
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<td>Time between 1st and 2nd bleed</td>
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<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>B.D.</td>
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<tr>
<td>L.F.</td>
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<td>R.G.</td>
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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 thrombo-
elastogram, and euglobulin lysis test.

(2) If so, do they have any prognostic
implications regarding gross mortality and
rebleeding from aneurysms? The only correla-
tion made between gross mortality and the test
values was noted in the fibrinogen determina-
tion. It was suggested that patients with fibrino-
gen 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 mecha-
nisms as therapy to prevent rebleeding, there
was no evidence of increased fibrinolytic activity.

These observations have direct implica-
tions regarding the use of aminocaproic acid or
other fibrinolytic inhibitors for the treatment of
subarachnoid hemorrhage in hopes of prevent-
ing 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 them-
selves 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 follow-
ing 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
The author is indebted to Miss Phyllis Krull and Mrs.
Judy Montgomery for their invaluable laboratory
assistance.

References
1. Ettinger MG: Unpublished observation
2. De Vivo D, Kline E, Dodge PR: Influence of
human cerebrospinal fluid on blood coagula-
1965
3. Niewiarowski S, Hausmanowa-Petrusewicz,
Wegrzynowicz Z: Blood clotting factors in
(Nov) 1962
effects of normal cerebrospinal fluid on blood
clotting and fibroblast growth. J Surg Res 1 :
260-266 (Nov) 1961
5. Roberts HR, Astrup T: Content of tissue
activator of plasminogen in monkey tissues.
Thrombos Diothes Haemorrh (Stuttg) 1 : 376-
379, 1957
6. Moltke P: Plasminogen activator in animal
(June) 1958
7. Albrechtsen OK, Storm O, Classen M: Fibri-
holytic activity in some human body fluids.
in the central nervous system. Neurology 19:
47-52 (Jan) 1969
Coagulation Abnormalities in Subarachnoid Hemorrhage
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Stroke. 1970;1:139-142
doi: 10.1161/01.STR.1.3.139

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