Congenital Deficiency of Factor VII in Subarachnoid Hemorrhage

Maria Luisa Papa, MS; Giuseppe Schisano, MD; Antonio Franco, MD; Pierpaolo Nina, MD

Background  Factor VII is essential for coagulation activation by the extrinsic pathway. Hemorrhages of the central nervous system in patients with congenital factor VII deficiency seem to have a higher incidence compared with other congenital coagulopathies. The purpose of this paper is to report two rare cases of subarachnoid hemorrhage and factor VII deficiency.

Case Description  Two cases of women affected by a congenital deficiency of factor VII and subarachnoid hemorrhage are reported. Diagnosis was obtained by cerebral computer tomography; cerebral panangiography was normal. Complete coagulation studies were performed showing prothrombin time prolongation and factor VII deficiency. In one patient, family studies revealed the existence of a similar coagulation disorder.

Conclusions  We suggest routine coagulation studies in all patients with subarachnoid hemorrhage. Determination of factor VII activity might be performed in patients with normal activated partial thromboplastin time and prolonged prothrombin time. (Stroke. 1994;25:508-510.)

Key Words  • coagulation • genetics • subarachnoid hemorrhage

Intracranial aneurysm rupture is known as the most frequent cause of subarachnoid hemorrhage (SAH), while SAH of unknown etiology has been less frequently observed; other causes can be intracranial or intraspinal arteriovenous malformations, hemorrhages due to arterial hypertension, tumoral hemorrhages, and blood dyscrasia. Several coagulation disorders may cause intracranial hemorrhage.

In the present paper two cases are reported in which SAH seems to be due to factor VII (FVII) congenital deficiency. The rare association between FVII deficiency and intracranial hemorrhage has been reported in the literature. Ragni et al. carried out a study of 12 cases taken from the literature that included three personal cases. Nearly all patients were children, except for one adult woman. Later, Hassan et al. reported the case of a woman with intracranial hemorrhage and FVII deficiency.

FVII is essential for coagulation activation by the extrinsic pathway. The presence of a tissue factor acting as cofactor is required for FVII activation. FVII deficiency was first described as a hemorrhosis congenital disorder in 1951 by Alexander et al. The hereditary character of this disorder has been recently confirmed by means of family studies; therefore, it is now generally agreed that it is transmitted as a recessive autosomal trait with phenotypic expression just in the homozygotes.

Case Reports

Case 1

A woman aged 30 years suddenly had a headache and vomited. On admission, 24 hours after the onset of the symptoms, nuchal rigidity was observed, but the neurological examination was otherwise normal. A computed tomographic (CT) scan showed the presence of blood in the subarachnoid space. The presence of an intracranial malformation was excluded by panangiography. The patient's coagulation study is shown in the Table. The patient was treated with a concentrate of FVII (PROVERTIN-UM TIM 3, IMMUNO AG, Vienna) because FVII deficiency had been observed; she was also treated with tranexamic acid, aprotinin, and dexamethasone. The meningeal syndrome disappeared within a week. A second coagulation study performed 9 days later showed a normalization of values. The patient was discharged after a normal neurological examination. It was not possible to carry out a study on her family tree.

Case 2

A woman aged 17 years complained of diffuse pain and some hours later showed a generalized convulsive state. A neurological examination showed moderate coma and bilateral Babinski reflex. Lumbar puncture revealed a slightly xanthochromic cerebrospinal fluid, while a CT scan with contrast demonstrated a diffuse SAH. An intracranial malformation was excluded by panangiography. A coagulation study was carried out (see Table). Blood was detected in the urinalysis. Ecchymosis was observed on the four limbs. On the second day a new convulsive state was observed. The patient was treated with a concentrate of FVII (PROVERTIN-UM TIM 3) tranexamic acid, aprotinin, mannitol, and dexamethasone. The values from the coagulation study performed on the second day were normal, including the FVII dosage. The patient's neurological condition worsened. A new lumbar puncture excluded rebleeding. Death occurred 48 hours after the onset of symptoms. Permission for an autopsy was not obtained. After the patient's death, a study of her family tree was carried out to assess the existence of similar coagulation disorders in other members of the family (Figure).
Coagulation Studies in Patients 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time, min</td>
<td>5</td>
<td>7</td>
<td>2-9</td>
</tr>
<tr>
<td>Platelet count, x10/L</td>
<td>250</td>
<td>274</td>
<td>150-350</td>
</tr>
<tr>
<td>Normotest, %</td>
<td>30</td>
<td>35</td>
<td>70-130</td>
</tr>
<tr>
<td>Thrombotest, %</td>
<td>25</td>
<td>25</td>
<td>70-130</td>
</tr>
<tr>
<td>Prothrombin time, s</td>
<td>17</td>
<td>18.6</td>
<td>12-14.5</td>
</tr>
<tr>
<td>Prothrombin time, s (patient+normal)</td>
<td>13</td>
<td>14</td>
<td>12-14.5</td>
</tr>
<tr>
<td>APTT, s</td>
<td>30</td>
<td>28</td>
<td>27-35</td>
</tr>
<tr>
<td>Fibrinogen, mg/100 mL</td>
<td>250</td>
<td>402</td>
<td>200-400</td>
</tr>
<tr>
<td>Thrombin time, s</td>
<td>22</td>
<td>18.6</td>
<td>17-23</td>
</tr>
<tr>
<td>Factor VII activity, U/dL</td>
<td>25</td>
<td>16</td>
<td>60-120</td>
</tr>
<tr>
<td>Factor VII antigen, U/dL</td>
<td>20</td>
<td>27</td>
<td>65-135</td>
</tr>
<tr>
<td>FDP serum, μg/mL</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td></td>
</tr>
<tr>
<td>CSF-FDP, μg/mL</td>
<td>&lt;20</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td>Factor II activity, U/dL</td>
<td>95</td>
<td>81</td>
<td>60-120</td>
</tr>
<tr>
<td>Factor IX activity, U/dL</td>
<td>102</td>
<td>98</td>
<td>60-120</td>
</tr>
<tr>
<td>Factor X activity, U/dL</td>
<td>82</td>
<td>76</td>
<td>60-120</td>
</tr>
</tbody>
</table>

APTT indicates activated partial thromboplastin time; FDP, fibrin/fibrinogen degradation products; and CSF, cerebrospinal fluid.

Results of Coagulation Studies

Screening clotting studies revealed abnormal prothrombin time, Normotest and Thrombotest, whereas the activated partial thromboplastin time, thrombin time, fibrinogen level, and platelet count were within the normal range. No inhibitors were present in the plasma of the patients since the addition of normal plasma in equal amount corrected the defect (Table). The FVII activity of case 1 gave a value of 25 U/dL and FVII antigen was 20 U/dL. The values of case 2 were 16 U/dL for the factor VII activity and 27 U/dL for the factor VII antigen. The results of assays of vitamin K-dependent factors were normal.

The studies on family members of patient 2 revealed borderline values of FVII (both activity and antigen) for the patient’s father. Similar values are compatible with the condition of heterozygosis found also in two brothers (III, 6; III, 9) and in her paternal uncle and her cousins (III, 1; III, 2; III, 5).

Discussion

In the literature several reports of SAH of unknown etiology can be found. Juul et al carried out a study of 32 patients suffering from SAH of unknown etiology; in four of them a study was performed of hereditary factors and previous diseases of their patients’ relatives affected by intracranial hemorrhage. These intracranial hemorrhages are likely to be linked to coagulation factor disorders.

Ragni et al published a study of 12 cases of intracranial hemorrhage caused by FVII deficiency, three of which were personal cases; the other nine, mainly children, were taken from the literature. According to this study, hemorrhages in the nervous system occurred in 16% of patients with FVII deficiency. Only 4 of the 12 patients survived.

In the Italian case, a woman with FVII deficiency who survived an intracranial hemorrhage was reported.

Diagram showing pedigree of patient 2 and coagulation studies performed on members of the family. N.S. indicates not studied; o, normal female; n, normal male; o, female heterozygote; o, male heterozygote; and e, female homozygote.
Patients with congenital FVII deficiency show hemorrhages of the central nervous system more frequently than other congenital coagulation disorders except for fibrinogen and FVIII deficiencies. It is important to underline that in the literature very few cases of SAH in adult patients are reported, yet both our patients are adults.

Our two patients had not shown any hemorrhagic symptoms before the SAH. They both showed a slight FVII deficiency, and this level of deficiency does not seem to be related to the clinical picture, which is also pointed out in the literature. Laboratory examinations confirmed congenital FVII deficiency by means of routine coagulation tests, specific assays of single vitamin K-dependent factors, and the exclusion of the presence of an acquired coagulation inhibitor.

Family studies of patient 2 reveal a genetic FVII reduction. The patient's father is heterozygote like his brother, and heterozygosis is found in the patient's brothers and cousins. The coagulation disease, which appeared phenotypically in our patient, seems to indicate a homozygous state, leaving room for the hypothesis of a new gametic mutation in her mother at the level of the FVII structural gene localized in chromosome number 13.

In conclusion, a complete coagulation study in patients affected by SAH is suggested, particularly when the panangiography is normal. FVII should be assayed in patients with normal activated partial thromboplastin time and prolonged prothrombin time. Moreover, it is worth emphasizing that FVII congenital deficiency is frequently observed in the Neapolitan area; in a school population between 9 and 12 years of age, a percentage of 3.4% was found.

References
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