Case report:
Isolated acquired factor VII deficiency: Report of Two Cases and Review of the Literature

Sylvie MN Mulliez, Pharm¹, Anna Vantilborgh, PhD² and Katrien MJ Devreese, MD, PhD¹

¹Coagulation Laboratory, Ghent University Hospital, Ghent, Belgium
²Department of Hematology, Ghent University Hospital, Ghent, Belgium

Case report

Case 1

A 54-year-old man was admitted with sudden onset of headache with vomiting and diarrhoea without neurological failure. Computer tomography (CT-scan) confirmed the diagnosis of a subarachnoid bleeding. Cerebral angiography could not show an aneurysm or other cause of bleeding.

During the admission period a spontaneous International Normalized Ratio (INR) elevation was seen. Over a period of 7 days the prothrombin time (PT) decreased from 70% towards 37% (normal range, 70-120%), unresponsive to two doses of intravenous vitamin K (5 mg and 20 mg) (Figure 1). The activated partial thromboplastin time (aPTT) was normal. The nature of the deregulated PT was further investigated by clotting factor dosage. Factor assays revealed normal factor levels of FII, FV, FIX and FX, but a low FVII (8%). In de diagnostic work-up, we performed a mixing study that showed a correction of the PT, suggesting the presence of factor deficiency. The Bethesda assay could not demonstrate a neutralizing inhibitor. Lupus anticoagulant (LA) testing was positive in the dilute Russel’s Viper Venom Test (dRVVT) (LA screen, Life Diagnostics, DSRV, Clarkstons, USA), the mixing test and confirmation test (LA confirm, Life Diagnostics) and negative in the aPTT system (PTT-LA, Diagnostica Stago, Asnières, France).

These results were compatible with an acquired FVII deficiency without inhibitory antibodies. Causes of FVII deficiency were ruled out: vitamin K deficiency, liver disease and diffuse intravascular coagulation (DIC). In this patient no underlying associated disease could be identified, the patient showed no signs of infection (C-reactive protein (CRP) of 4.7 mg/L, normal range <5 mg/L) and malignancy was excluded.

The patient was initially transfused with 2 units fresh frozen plasma. After 20 days the PT normalized spontaneously to 76% and LA disappeared after one month. FVII slowly normalized to 41% after 20 days, 60% after three months and 78% after seven months.

Figure 1. Prothrombin time (PT) of case 2 during hospital admission. The arrows indicate the moments of vitamin K administration, first time 5 mg and the second time 20 mg, without any response in PT.
**Case 2**

In September 2014, a 78-year-old man presented to the emergency department with red blood loss per anum. Since four days he had melena and complained of low-grade fever, sweats, generalized malaise since a few weeks and 5 kg weight loss during the last months. He had a medical history of rheumatoid arthritis treated with methotrexate and folic acid. In 2012 he was diagnosed with prostate cancer with solitary bone metastasis, followed by prostatectomy with lymphadenectomy and radiotherapy. In August 2014, PET-CT and PSA results (<0.03 µg/L) showed no relapsed prostate cancer. At admission, a physical examination revealed an enlarged axillary lymph node on the right side and multiple other lymphadenopathies supra- and infra-diaphragmatic. A lymph node biopsy was taken.

At presentation the complete blood count revealed a white cell count (WBC) of 1.52*10^9/L (normal range, 3.65-9.30*10^9/L), platelet count of 148*10^9/L (normal range, 149-319*10^9/L) and haemoglobin value of 118 g/L (normal range, 129-173 g/L). The coagulation results showed normal aPTT of 35.1 sec (normal range, 28.9-38.1 sec) and normal PT of 77% (normal range, 70-120%) with an INR of 1.18 (normal range, 0.9-1.1). Lymph node biopsy results were consistent with the diagnosis of classical Hodgkin’s lymphoma, type mixed cellularity.

During the admission period a deterioration of the coagulation results was seen. Two days after admission a PT of 62% and an aPTT of 46 sec was observed. Factor assays revealed normal level of FV, FVIII, FIX, FXI and FXII, FIII and a borderline normal value of FX (65%), FVII was reduced (35%). The reduced FVII was confirmed in a second sample (30%). The mixing study showed a correction of the PT, suggestive for the presence of a factor deficiency. Lupus anticoagulant (LA) testing was only positive in the aPTT system (screen and mix with PTT-LA and confirm with Staclot-LA® assay (Diagnostica Stago, Asnières, France)), and negative in the dRVVT system (LA screen and LA confirm). On the moment of LA testing, the CRP was 63.5 mg/L, therefore the LA testing should be interpreted with care since Staclot-LA® can be false positive if CRP is elevated [3]. Twelve days later LA was negative.

Vitamin K deficiency could be ruled out because of the isolated decrease of FVII. There was no evidence for DIC (high fibrinogen levels). Aspartate– and alanine aminotransferase (AST and ALT) were slightly elevated, respectively 51 U/L (normal range, 0-37 U/L) and 43 U/L (normal range, 7-40 U/L), but did not correlate with the PT prolongation during the hospitalisation.

We concluded to an acquired FVII deficiency without inhibitor associated with Hodgkin’s lymphoma. He was treated accordingly with methylprednisolone and chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine). After two weeks the PT normalised.

**Discussion**

We describe two patients diagnosed with an isolated acquired factor (F) VII deficiency, without inhibitor. We report what is currently known about the pathogenesis, clinical features, diagnosis, treatment and prognosis of acquired FVII deficiency. After a literature search we found 22 individual cases reported in the literature (between 1980 and July 2014). Besides, Toor et al. identified eight patients with acquired FVII deficiency within two weeks following hematopoietic stem cell transplantation and Biron et al. reported eleven cases of acquired FVII deficiency associated with severe systemic sepsis [1,2].

**Pathogenesis**

In a minority of the cases of acquired FVII deficiency (nine patients) an inhibitory antibody to FVII has been described [4-12]. In these cases the PT remained prolonged after mixing of the patient plasma with normal pooled plasma. The inhibitor antibody was of the immunoglobulin G (IgG) type, with features of IgG1 with κ and λ-light chains inhibiting the procoagulant activity of activated FVII (FVIIa) by interaction with the light chain. They also suggested that the antibody recognizes the calcium-dependent conformation in or near the Gla domain having the ability to inhibit the interaction between FVIIa and tissue factor (TF) or phospholipid membranes [7,9,11,13].

In the cases where no neutralizing auto-antibody could be demonstrated in vitro different pathophysiological hypothesis have been suggested. An IgG autoantibody without inhibitory activity may enhance in vivo clearance of FVII by formation of immune complexes or FVII could be absorbed from blood by binding to either the antibody-producing lymphoid cells or to tissue deposits or the antibody may bind to cells secreting factor VII and thereby down regulating its synthesis by feedback mechanism [14-15]. In the context of sepsis, FVII consumption is suspected due to tissue factor (TF) overexpression by monocytes and endothelial cells or a enzymatic degradation of FVII by proteases (cathepsin G and human leucocyte elastase) released from activated granulocytes in sepsis have been postulated [2]. An alternative explanation for the apparent loss of FVII after stem cell transplantation was speculated: high-dose chemo-radiotherapy induces an increased
vascular permeability enhancing access of intravascular FVII to a large pool of extravascular TF capturing FVII in the extravascular compartment [1]. In malignancy, the possibility that FVII is eliminated from the circulation by abnormal fixation to tumor cells was assumed [16-18].

In 33 out of 41 cases described in the literature, information about LA is lacking. In six out of eight cases from whom information was reported, LA was present [1,4,10]. In one of our reported cases LA testing was also positive. The precise role of the lupus inhibitor remains unclear.

**Patient’s characteristics**

Considering all cases (n=43), at disease onset the median age was 38 years (range: 2.8 – 80 years). Four out of these 43 cases were described in the pediatric age group (9%) [1,21,22]. The disease affects males more often than females, with an overall male: female ratio of 2.3:1 (30 men and 13 women) [1,4-12,14-27].

**Underlying diagnosis**

The most frequently associated diseases of acquired FVII deficiency are severe systemic sepsis (16 cases), malignant diseases (8 cases) (solid tumors, acute leukemia and lymphoproliferative malignancies) and stem cell transplantation (8 cases) [1-2,5,7,11,15-22,25-26].

**Clinical features**

Bleeding occurred in 47% (20 out of 43) cases. Most cases (19 of 20 cases) experienced severe bleeding, including vaginal bleeding, pulmonary and digestive tract hemorrhage, hematuria and intracerebral hematoma [1,4,6-8,10,12,14,15,20,24,29].

**Diagnosis**

Acquired factor VII deficiency is most often diagnosed in patients with discordance between a prolonged PT and a normal aPTT. Occasionally the aPTT can be prolonged in the presence of LA (six cases described) [1,4]. As a diagnostic step, coagulation factor activity should be determined and an isolated decrease of FVII level should be confirmed. The median FVII level reported in the case studies was 17% (range <1%-50%) [1,4,7,9-12,14-26]. To further investigate the FVII deficiency, mixing study should be performed. If the PT remains prolonged after mixing of patient plasma with normal pooled plasma, a factor inhibitor is suspected. The Bethesda assay may confirm the presence of a specific FVII inhibitor.

**Treatment & outcome**

The treatment and outcome reported in respectively 32 and 29 out of 43 cases is summarized in Table 1. Currently, there are no standardized guidelines for the treatment of acquired FVII deficiency. The initial therapeutic choice must be made based on the biological features and clinical severity of bleeding. Besides, the underlying disorder which might be associated has to be treated. When antibodies are present and persist, immunosuppression is recommended to eradicate the inhibitor.

The overall clinical outcome of FVII deficiency is poor, complete remission was seen in only 17 out of 29 patients (59%) [1,6,7,14,15,17,19-25,29]. Bleeding complications were the direct cause of death in four patients (intracranial, gastrointestinal and pulmonary hemorrhage) (13%) [1,8,12].

Table 1. Treatment and outcome reported in 33 cases of acquired FVII deficiency.

<table>
<thead>
<tr>
<th>First author (year)/Ref</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1/PR</td>
<td>Vit K</td>
<td>CR after 7 months</td>
</tr>
<tr>
<td>Case 2/PR</td>
<td>Methylprednisolone</td>
<td>CR after 24 days</td>
</tr>
<tr>
<td>Anoun (2014)/[12]</td>
<td>FFP (10ml/kg for 2 days)</td>
<td>Death, cause of death: intracranial hemorrhage on day 15</td>
</tr>
<tr>
<td>Bidet (2009)/[19]</td>
<td>Vit K</td>
<td>CR when infection disappeared</td>
</tr>
<tr>
<td>Granger (2009)/[22]</td>
<td>Vit K and FFP (15 ml/kg) before surgery</td>
<td>CR 5 days after surgery</td>
</tr>
</tbody>
</table>
| Lim (2006)/[4]         | 1. Vit K, FFP (15ml/kg), tranexamic acid  
<pre><code>                    | 2. rFVIIa | Death, cause of death: progressive multiorgan failure |
                    | 2. FVII (FVII-LFB®) during 10 days | CR after 14 days |
</code></pre>
<p>| Zili (2005)[18]        | FFP (1ml/kg) (before and after surgery) | ND |</p>
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Treatment Details</th>
<th>Outcome Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang (2004)/[24]</td>
<td>1. Vit K, FFP 2. rFVIIa 3. rFVIIa restarted on day 10 due to new focus of hemorrhage</td>
<td>CR after 48 days</td>
</tr>
<tr>
<td>Mullighan (2004)/[15]</td>
<td>1. Vit K, FFP (3 U every 8h), aminocaproic acid (1g/h IV after loading dose of 5g) 2. rFVIIa before and after surgery</td>
<td>CR</td>
</tr>
<tr>
<td>Aguilar (2003)/[5]</td>
<td>Tranexamic acid and methylprednisolone</td>
<td>Death, cause of death: cardiorespiratory failure on day 15</td>
</tr>
</tbody>
</table>
| Toor (2002)/[1] | All eight patients: vit K Two patients: FFP One patient: plasma exchange with FFP replacement | Death, cause of death: fungemia on day 23  
Death, cause of death: ARDS on day 15  
CR  
Death, cause of death: hepatorenal syndrome on day 22  
Death, cause of death: sepsis and GVHD = cause of death on day 22  
Death, cause of death: GI bleeding on day 18  
CR  
Death, cause of death: pulmonary hemorrhage on day 17 |
| Okajima (1999)/[6] | 1. FFP ineffective 2. Methylprednisolone (1g for 3 days followed by tapering doses) | CR |
| Ranchère (1999)/[17] | FVII-LFB* | CR |
| White (1999)/[20] | rFVIIa | CR after 8 weeks |
| Muleo (1998)/[25] | rFVIIa and antifibrinolytic therapy | CR after chemotherapy |
| Brunod (1998)/[7] | 1. Blood transfusion, FFP, FVII-LFB* 2. Methylprednisolone (1mg/kg/day) and heparin | CR after 8 days |
| de Raucourt (1994)/[16] | 1. Vit K 2. FVII concentrate before surgery, no bleeding complications occurred, 3. IVIg (0.4 g/kg/day for 5 days) | Death, patient died from disease progression 6 weeks later |
| Mehta (1992)/[8] | FFP (800 ml) | Death, cause of death: intracerebral haemorrhage and large haematoma in the wall of the larynx on day 2 |
| Alsar (1990)/[26] | Vit K | Death |
| Delmer (1989)/[9] | 1. FFP (2 Units) 2. IVIg (0.4 g/kg/day for 5 days) 3. Cyclophosphamide (1.5 g in bolus IV for 1 day) and corticosteroids (methylprednisolone 500 mg/day for 2 days, following by prednisolone 100 mg/day) 4. Plasma exchanges with FFP replacement, FVII concentrate and antitrombin III before surgery 5. Tapering prednisolone | 1. Relapse 1 month later, but no plasma inhibitory activity was evidenced at that time  
2. CR |
We described two patients with acquired FVII deficiency followed by a literature search on case reports presenting patients with acquired FVII deficiency. Acquired FVII deficiency is a rare disease, with only 41 patients reported in the literature so far, but the incidence might be underestimated. We found 22 individual case reports, eight patients with acquired FVII deficiency following hematopoietic stem cell transplantation and eleven cases associated with severe systemic sepsis. The exact pathogenesis of the disease is still unknown, but different pathophysiological hypotheses have been suggested. Bleeding occurs in about half of the cases. Patients without prior clinical evidence of bleeding were diagnosed based on coagulation abnormalities during routine blood screening. The diagnose for this acquired hemorrhagic disorder should be suspected when an isolated PT prolongation is seen.

References


27. Sciascia S, Sanna G, Murru V, Roccatallo D, Khamasha MA, Bertolaccini ML. Anti-prothrombin (aPT) and anti-phosphatidylycerine/prothrombin (aPS/PT) antibodies and the risk of thrombosis in the antiphospholipid syndrome. A systematic review. *Thrombosis and haemostasis* 2014; 111: 354-64.
