Factor VII Deficiency Presenting with Subarachnoid Hemorrhage: A Rare Case Report

Subaraknoid Kanama ile Başvuran Faktör VII Eksikliği: Nadir Bir Olgu Sunumu

Sumaiyah Adzahar[1,2,3], Dhamirah Nazihah Mohd Nasiruddin[1,2,4], Zefarina Zulkafli[1,2], Salfarina Iberahim[1,2]

[1]Department of Hematology & Transfusion Medicine Unit, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[2]Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia
[3]Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), 20400 Kuala Terengganu, Terengganu, Malaysia.
[4]Department of Pathology & Laboratory Medicine, Faculty of Medicine, International Islamic University Malaysia, 25200 Kuantan, Pahang, Malaysia.

ABSTRACT

Factor VII (FVII) deficiency is a rare inherited bleeding disorder affecting about 1 in 500 000 individuals. It has a wide range of clinical presentations, from moderate or even asymptomatic forms that do not correlate well with FVII plasma levels to severe and potentially fatal bleeding. As a result, dealing with FVII-deficient patients during surgery or for long-term prophylaxis is difficult. Laboratory testing for FVII activity, in addition to clinical history, is the first-line method for diagnosing FVII deficiency and aids in patient management.

Keywords: Inherited factor VII deficiency, intracranial hemorrhage, diagnosis, treatment

Received: 01.13.2022 **Accepted:** 03.16.2022

ÖZET

Faktör VII (FVII) eksikliği, yaklaşık 500.000 kişiden 1'ini etkileyen, nadir görülen kalıtsal bir kanama bozukluğudur. FVII plazma seviyeleri ile iyi korelasyon göstermeyen orta ve hatta asemptomatik formlardan ciddi ve potansiyel olarak ölümcül kanamaya kadar geniş bir klinik sunum yelpazesine sahiptir. Sonuç olarak, ameliyat sırasında veya uzun süreli profilaksi için FVII eksikliği olan hastalarla uğraşmak zordur. FVII aktivitesi için laboratuvar testleri, klinik öyküye ek olarak, FVII eksikliğini teşhis etmek için birinci basamak yöntemdir ve hasta yönetimine yardımcı olur.

Anahtar Sözcükler: Kalıtsal faktör VII eksikliği, kafa içi kanama, tanı, tedavi

Geliş Tarihi: 13.01.2022 **Kabul Tarihi:** 16.03.2022

ORCID IDs: S.A. 0000-0003-3378-1897, D.N.M.N.0000-0002-4764-1361,Z.Z.0000-0003-2029-2234,S.I.0000-0002-6903-3519

Address for Correspondence / Yazışma Adresi: Sumaiyah Adzahar, Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), 20400 Kuala Terengganu, Terengganu, Malaysia. E-mail: srikandimaya11@gmail.com

doi:http://dx.doi.org/10.12996/gmj.2022.44

INTRODUCTION

Factor VII (FVII) deficiency is the most common among rare bleeding disorders, with an estimated prevalence of 1 in 500 000 worldwide. It is inherited in an autosomal recessive pattern and manifests in various clinical symptoms. Because it is clinically expressed in homozygotes or compound heterozygotes, it is more common in a population where consanguineous marriages are common (1). Factor VII levels of less than 1% frequently present with bleeding symptoms similar to those of hemophilia, while levels of 5% or more present with milder symptoms, such as epistaxis, menorrhagia, and bruising (2). Here, we report a rare case of FVII deficiency who develops subarachnoid hemorrhage (SAH) secondary to a ruptured aneurysm.

CASE REPORT

A 48-year-old woman was transported to our hospital unconscious, and she regained consciousness five minutes after arrival. On further history, it was found that she had a throbbing headache associated with vomiting for two weeks. She had no underlying medical conditions such as hypertension or diabetes, no personal or family history of bleeding disorders, trauma or medication use. Physical examination showed normal vital signs with a blood pressure of 129/60mmHg, no evidence of skin ecchymosis, petechiae, or other areas of bleeding, and her neurological findings were normal. A computed tomography scan showed generalized SAH. Subsequently, computed tomography angiography revealed a ruptured aneurysm in the internal cerebral anterior to the posterior communicating artery. The patient was scheduled for an emergency aneurysm clipping.

Routine preoperative blood tests showed an isolated prolonged prothrombin time (PT) of 21.4 s (normal range: 12.6 – 15.7s). The patient's activated partial thromboplastin time (aPTT), platelet count, liver function, and renal function was normal. Normal plasma mixed with the patient's plasma partially corrected the PT. At that stage, coagulation factor deficiency or an inhibitor was considered a possible cause. Coagulation factors and lupus anticoagulants were checked, as lupus anticoagulants are by far the most common inhibitors affecting PT. Dilute Russell's viper venom time was normal, making a lupus anticoagulant highly unlikely. A factor assay revealed a marked FVII deficiency (10%; normal range: 50 – 150%). Other factors (factors II, V, and X) were normal. Bethesda assays were negative for factor inhibitors.

To prevent excessive bleeding during surgery, the FVII level of 15–25% was targeted. Preoperatively, the patient received recombinant factor VIIa (rFVIIa) at a 15 mcg/kg dose. Intraoperatively, she received three doses of rFVIIa and four units of fresh frozen plasma (FFP) until hemostasis was secured. The surgery went well, with minimal bleeding. Upon discharge, the patient was well with no bleeding complications. On a six-month follow-up, the patient's FVII level remained low (13.1%). The patient was diagnosed with FVII deficiency, most likely congenital. Her baseline and six-month postoperative FVII levels are shown in Table 1.

Table 1: The patient's factor VII levels (Normal range: 50–150%)

On admission	Six months after surgery
10 %	13.1 %

DISCUSSION

Factor VII deficiency was first reported in 1951 by Alexander et al. Factor VII is a vitamin K–dependent serine protease produced in the liver and circulates approximately 99% as inactived zymogen, while 1% in activated FVII (FVIIa) form. Upon vessel injury, tissue factor (TF) is exposed and binds both FVII and activated FVIIa (FVIIa). The TF-FVIIa complex then activates FX and FIX to facilitate low-level thrombin generation, resulting in stable fibrin clots (3).

Type I or II inherited FVII deficiency is determined by the presence or lack of FVII antigen in plasma. Type I deficiencies (quantitative defects) result from decreased production or accelerated clearance of FVII, while a dysfunctional molecule causes type II (qualitative defects) deficiencies.

Acquired FVII deficiency is far more common than inherited deficiency (4) and may arise due to vitamin K deficiency, vitamin K antagonist therapy or liver disease.

FVII deficiency has a wide range of clinical manifestations ranging from severe to mild or even asymptomatic forms (5). Mortality is related to severe bleeding, most often resulting from intracranial bleeding (ICB) as was seen in the index case. Few cases involving ICB have been reported in the literature. Ragni et al. reported 12 cases of ICB caused by FVII deficiency, with nervous system haemorrhages occurring in 16% of the patients and only four patients surviving (6). Papa et al. reported two cases of women presenting with SAH due to FVII deficiency (7). It is noteworthy that very few cases of SAH in adults due to FVII deficiency have been reported. In contrast to these reports, we identified FVII deficiency in an adult woman who develops SAH secondary to a ruptured aneurysm. Our case is rare, and the patient survived.

Factor VII deficiency can be suspected when a coagulation screening shows isolated prolongation of the PT with a normal aPTT. The PT prolongation is corrected with normal pooled plasma mixed with the patient's plasma (mixing study). Factor VII deficiency is usually characterized by an FVII:C of <70% (0.7 IU/mL), although clinically relevant manifestations mainly appear when FVII:C is <30% (clinical manifestation threshold) (8). To confirm the diagnosis, the FVII assay should be repeated at least once (9). Assays for other vitamin K–dependent clotting factors are not necessary, but they are helpful to rule out combined deficiencies of vitamin K–dependent factors. In such cases, however, the aPTT is also prolonged (4).

The treatment decision depends on the severity of FVII deficiency and the severity of bleeding or surgery (1). Currently, there are several options for FVII replacement. Antifibrinolytics and local fibrin glue are usually used as supportive and adjunctive hemostatic therapies. In countries where concentrated products are unavailable, fresh frozen plasma (FFP) is still used. Prothrombin complex concentrates (PCCs) are plasma-derived virally inactivated products containing factors II, IX, and X and variable amounts of FVII. A dosage of 20–30 IU/kg is recommended. Recombinant FVIIa (NovoSeven) superseded the alternatives of FVII concentrate, PCC, and FFP in preventing and treating bleeding (9).

CONCLUSION

Inherited FVII deficiency may be contributed to intracranial bleeding secondary to a ruptured aneurysm. The case reported herein suggests that there are probably many more individuals with congenital deficiencies who may never be diagnosed because they are otherwise asymptomatic and healthy. Awareness of this condition is crucial for early diagnosis and treatment.

Conflict of interest
No conflict of interest was declared by the authors.

Acknowledgment
We thanked the Universiti Sains Malaysia for the Short Term Grant (304/PPSP/6315414) provided for this case report.

REFERENCES

1. Shams M, Dorgalaleh A. Congenital factor VII deficiency. Congenit Bleeding Disord Diagnosis Manag. 2018;239–59.
2. Ciantar E. Factor VII Deficiency in Pregnancy and Labour: A Case Report. Obstet Gynecol Int J. 2014;1(1):9–10.
3. Mumford AD, Ackroyd S, Alikhan R, Bowles L, Chowdary P, Grainger J, et al. Guideline for the diagnosis and management of the rare coagulation disorders: A United Kingdom haemophilia centre doctors' organization guideline on behalf of the British committee for standards in haematology. Br J Haematol. 2014;167(3):304–26.
4. Napolitano M, Siragusa S, Mariani G. Factor VII deficiency: Clinical phenotype, genotype and therapy. J Clin Med. 2017;6(4):11–4.
5. Salcioglu Z, Akcay A, Sen HS, Aydogan G, Akici F, Tugcu D, et al. Factor vii deficiency: A single-center experience. Clin Appl Thromb. 2012;18(6):588–93.
6. Meeks SL. Factor VII Deficiency. Transfus Med Hemost Clin Lab Asp Second Ed. 2013;88:723–4.
7. Papa ML, Schisano G, Franco A, Nina P. in Subarachnoid Hemorrhage. 1993;508–10.
8. Sevenet PO, Kaczor DA, Depasse F. Factor VII Deficiency: From Basics to Clinical Laboratory Diagnosis and Patient Management. Clin Appl Thromb. 2017;23(7):703–10.
9. Robinson KS. An overview of inherited factor VII deficiency. Transfus Apher Sci. 2019;58(5):569–71.