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Cerebral venous sinus thrombosis in a patient with undiagnosed factor VII deficiency

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CASE REPORT

Cerebral Venous Sinus Thrombosis in a Patient with Undiagnosed Factor VII Deficiency

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Abstract

Factor VII (FVII) deficiency is one of the rare inherited bleeding disorders. Thrombosis has been occasionally described in inherited FVII deficiency. Here, we report a young female with undiagnosed FVII deficiency who presented with cerebral venous sinus thrombosis (CVST). Oral contraceptive pill was found to be prothrombotic risk factor. The CVST occurred in spite of the congenital FVII deficiency indicating that no definitive antithrombotic protection is assured by this defect. Low molecular weight heparin and anti-Xa assay were found to be safe choice of anticoagulation and monitoring, respectively, in this patient.

Key Words: *Factor VII. Thrombosis. Cerebral venous sinus.*

INTRODUCTION

Inherited factor VII (FVII) deficiency is one of the rare inherited bleeding disorders, with an approximate prevalence of about 1 in 500,000 in its severe form, to one in 350 in the heterozygous state.[1,2] In Pakistan, inherited FVII deficiency is one of the commonest rare bleeding disorders, in part, due to traditional consanguineous marriages.[3]

Factor VII deficiency presents with a wide clinical heterogeneity characterized by poor correlation of factor level with bleeding.[4] Clinical features are variable ranging from mild or even asymptomatic forms to lethal cerebral hemorrhages. Paradoxically, besides bleeding FVII deficiency is also associated with thrombosis. Both venous and arterial thrombosis has been reported in approximately 3 to 4 percent of patients with FVII deficiency.[5] Most of these have been reported after the use of factor replacement therapy or coexisting inherited or other acquired thrombotic risk factors.[6] In rare cases, FVII-deficient patients present with spontaneous thrombosis as well.

Here, we report a case of FVII deficiency and cerebral venous sinus thrombosis (CVST) and a review of management of such cases.

CASE REPORT

In September 2015, a 40-year female (gravidity 0, parity 0) with no known comorbids, presented to emergency with complaints of jerky movements in the left arm and headache for three days. Her past history was unremarkable apart from irregular menstrual cycles without menorrhagia for which she was taking tablet norethisterone, 5 mg, thrice daily for 21 days every month for past three months. There was no family or personal history of abnormal bleeding. Examination revealed decreased power of left upper limb only. Contrast enhanced computerized tomography (CT) scan of brain, done as a part of initial workup of abnormal limb movement and headache, showed deep CVST involving all sinuses more marked on the right side extending into the right internal jugular vein without intracranial haemorrhage or infarct (Figure 1).

Other routine laboratory workup showed haemoglobin 13 g/dl (normal: 11.1 - 14.5 g/dl), white blood cell count 14 x 10^9/L (normal: 4 - 1 0 x 10^9/L), platelets 337 x 10^9/L (normal: 150 - 400 x 10^9/L) and no abnormality detected

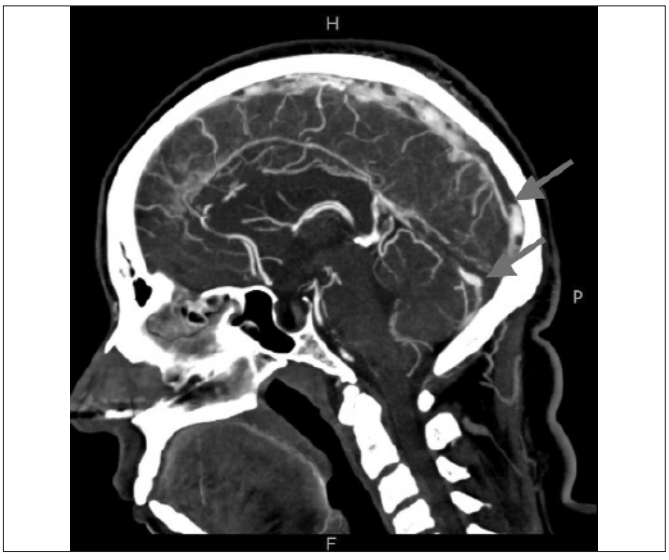

Figure 1: Sagittal view of skull showing filling defect (thrombus) involving all deep cerebral venous sinuses.

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on peripheral smear. Coagulation studies revealed prothrombin time (PT) 27 seconds (sec) (control 9-14 sec), INR 2.6 (control ratio ≤ 1) and activated partial thromboplastin time (APTT) 25 sec (control 25-35 sec). Liver function and renal profile was normal. ANA and anti-DNA tests were negative. Anticardiolipin IgM was 2.26 MPL unit/ml (normal range ≤ 7 MPL unit /ml). In view of incidental finding of prolonged PT in the absence of bleeding symptoms, PT mixing study was ordered that showed correction of PT with normal plasma (immediate and after incubation at 37°C for 2 hours) and aged serum. Subsequently, FVII level was checked and found to be 14%. The findings were suggestive of FVII deficiency.

Heritable thrombophilia workup was also performed and showed normal protein S: 85% (60-110%), protein C: 89% (normal: 72-160%), antithrombin III: 92% (normal: 80-120%) and activated protein C resistance: 0.92 (normal: 0.86-1.1 ratio). Homocysteine levels were found to be 12µmol/L (normal: 5 -12 µmol/L).

For CVST, the patient was started on subcutaneous injections of low molecular weight heparin (LMWH) Enoxaparin, 60mg, twice daily to which she responded well with improvement of presenting symptoms. Anticoagulation was monitored clinically and with anti-Xa assay. No FVII levels were repeated during follow-ups as there were no bleeding symptoms at all. During hospital stay and subsequent follow-ups in anticoagulation clinic, she remained well with normalization of left arm movement. Until the follow-up in December 2015, no bleeding was reported and anti-Xa remained in therapeutic range. The patient gave her informed consent prior to inclusion in the study.

DISCUSSION

A thrombotic manifestation in a patient congenitally predisposed to bleeding always represents an exceptional event. To date, occurrence of thromboembolic events in FVII-deficient patients have been reported in several individual cases and few case series; and in most of these cases, thrombosis was related to replacement therapies, surgical interventions, and delivery or heritable thrombophilia factors.[7,8] In this case, an oral contraceptive pill was considered to be an associated thrombotic risk factor. The workup for heritable, thrombophilia was found to be normal. However, prothrombin gene and factor V Leiden mutation could not be performed because our facility lacks this capacity. Therefore, the possibility of additional prothrombotic risk factors cannot be entirely excluded.

The type of underlying mutation of FVII like Arg294Val and Arg304Gln are also reported to be associated with thrombotic event.[9] In our case, amino acid sequencing and nucleic acid sequencing could not be performed due to non-availability of these tests at our setup.

In a study conducted by Mariani *et al*., thrombosis in FVII deficient patient was not associated with any specific phenotype, mutation zygosity or any specific factor level cut-off.[8] Hence, the exact cause of thrombosis in factor VII deficient patients still remains unclear.

International consensus guidelines for treatment modalities of the thromboembolic events in rare bleeding disorders are lacking. In addition, sparse information is found in literature related to the clinical management of thrombosis in inherited FVII deficiency. Arellano-Rodrigo *et al*. reported two cases highlighting the difficulty in management, where one of the patients experienced mucosal bleeding. Both the patients received warfarin as initial anticoagulation therapy.[10] Use of LMWH by Klovaite *et al*. for a FVII deficient patient with vena porta thrombosis was also associated with bleeding.[7] On the other hand, LMWH was found to be safe anticoagulation alternative in our patient. However, optimal doses and safety remain to be defined. In the same way, the safety profile of new direct oral anticoagulants needs to be investigated for treating thrombosis in rare bleeding disorders.

To conclude, we have reported the concomitant occurrence of CVST and a hemorrhagic disorder. This case supports previous observations and demonstrates that a risk of thrombosis should be considered in the presence of inherited FVII deficiency. However, the choice of anticoagulant treatment and prophylaxis needs to be defined.

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