

# Recurrent Intracranial Haemorrhages in A Patient with Factor Seven Deficiency: A Case Report

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## SUMMARY

Inherited factor VII (FVII) deficiency is a rare autosomal recessive hemorrhagic disorder. Clinical bleeding can vary widely and does not always correlate with the level of FVII coagulant activity measured in plasma. Most severe cases of factor VII (FVII) deficiency are diagnosed during childhood, often during the first 6 months of life. In infancy, the most common sites of bleeding occur in the gastrointestinal tract or CNS, accounting for 60-70% of bleeds in this age group. Recombinant factor VIIa (rFVIIa) is one such agent, which has been shown to prevent hematoma expansion and improve outcome in acute intracranial haemorrhages. The purpose of this case report is to share our experience regarding the usefulness of rFVIIa in the management of acute intracranial haemorrhage.

## KEY WORDS:

*Inherited factor VII, Intracranial haemorrhage, Recombinant factor VII (rFVII)*

## INTRODUCTION

Spontaneous intracranial haemorrhage has been associated with coagulopathy, vascular lesions, drug and haematological disorder calling for immediate intervention. It has been reported that the good results could be achieved by surgical operation for patients with intracranial haemorrhages when the underlying haematological disorders are in a state of remission. However, these patients were usually treated conservatively because of a high risk of massive bleeding due to coagulation difficulty during or after operation<sup>1</sup>.

## CLINICAL PRESENTATION

A 7 months old Malay boy who was known to have severe factor seven deficiency and partial aqueduct stenosis presented with recurrent episodes of intracranial haemorrhages after trivial trauma. His first presentation was at the age of two months old and the second one at the age of 6 months old. In both episodes he presented with a history of vomiting, irritability and lethargy. In addition to the factor VII deficiency, he also has ventriculomegaly secondary to aqueduct stenosis and a variant of the Dandy Walker Syndrome which is being managed expectantly. During both these presentations, he was treated conservatively by us and conjoint management with the haematologist. The patient was given FFP and Recombinant activated FVII (rFVIIa) during both occasions.

## DISCUSSION

### *Factor Seven Deficiency*

Inherited factor VII (FVII) deficiency is a rare autosomal recessive hemorrhagic disorder. Clinical bleeding can vary widely and does not always correlate with the level of FVII coagulant activity measured in plasma. Most severe cases of factor VII (FVII) deficiency are diagnosed during childhood, often during the first 6 months of life. In infancy, bleeding most commonly occur in the gastrointestinal tract or CNS, accounting for 60-70% of bleeds in this age group. Spontaneous haemarthrosis also presents more frequently in children younger than 5 years (occurring in 20% of patients with FVII deficiency). These children usually have FVII levels of less than 2%.

FVII is one of the vitamin K-dependent coagulation factors synthesized in the liver. It is present in plasma in low concentrations (0.5 mcg/mL) and has a short circulating half-life of 3-4 hours. Plasma FVII predominantly exists in the form of the inactive single-chain zymogen; however, approximately 1% circulates in the activated form (FVIIa). Activation of FVII is the initiating event of *in vivo* coagulation. The ability of FVIIa to cleave other clotting factors depends on binding to its cofactor tissue factor (TF), which is expressed on the surface of endothelial cells and monocytes in response to injury or inflammation. With formation of the TF/VIIa complex, FVIIa rapidly activates clotting factors VII, IX, and X, initiating the coagulation cascade.

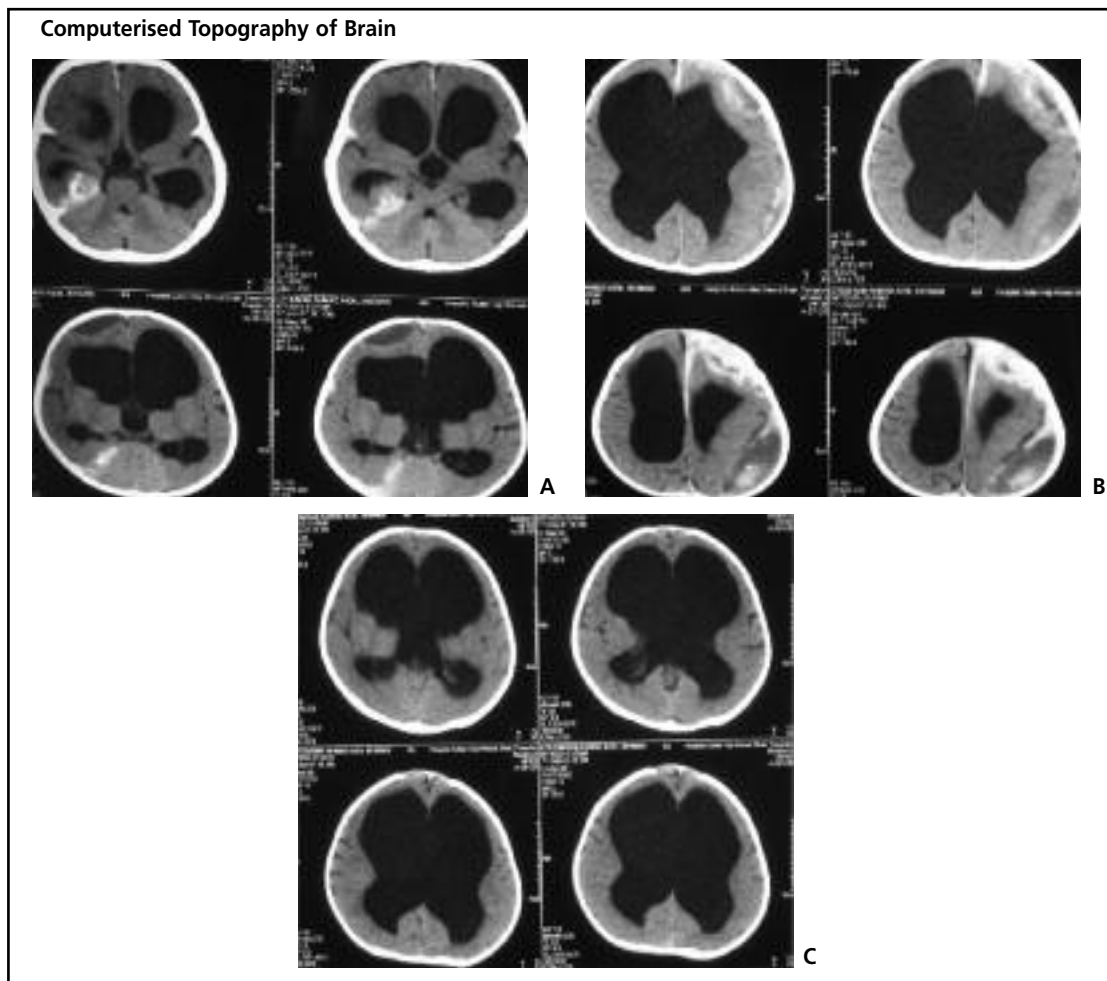
### *Pathophysiology*

Inherited FVII deficiency can be classified as type 1 or type 2, depending on the absence or presence of FVII antigen in plasma. Type 1 deficiencies result from decreased biosynthesis or accelerated clearance; type 2 abnormalities represent a dysfunctional molecule. More than 100 mutations, mostly missense mutations, have been identified in the FVII gene located on chromosome 13. Mutations have been identified throughout the gene, affecting all domains of the transcribed protein, most frequently the catalytic domain.

Correlations between the factor VII genotype, FVII clotting activity and the clinical phenotype are not tight. Although individuals with the lowest FVII levels are most likely to be symptomatic, patients with identical mutations may have marked differences in clinical bleeding, suggesting that other factors may contribute to the clinical manifestations of FVII deficiency. Investigations to determine the contribution by

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**Fig. 1:** A plain CT brain showing acute on chronic subdural haemorrhages when he was first time presented at the age of 2 months old (A). Different ages and locations of blood clots when presented a second time at the age of 6 months old (B). A repeat CT brain 2 months later showing the subdural haemorrhages already completely resolved after medical treatment (C).

FVII polymorphisms, other haemostatic proteins, and environmental factors have not yielded specific predictors of bleeding risk. At present, classification based on clinical history (age and type of presentation) rather than on FVII activity levels has proved to be more useful in predicting future risk of bleeding

*Treatment*

**Acute bleeds:** Management of acute haemorrhage primarily consists of factor VII (FVII) replacement therapy to treat bleeding. Levels of more than 10% are usually haemostatic, although higher levels may be advisable in the event of a severe bleeding episode. Because FVII has a short half-life of 3 to 4 hours, repeat treatment may be necessary in all except minor bleeding episodes. Apart from FVII replacement therapy, there are some other alternative treatments for this condition. Fresh frozen plasma is the least effective because of the volume required to provide adequate FVII replacement. No viral attenuation of this product means that a risk of viral transmission is present. Prothrombin complex concentrates contain factors II, IX, and X in addition to FVII. These concentrates have undergone viral attenuation during manufacturing. Determining the appropriate dosage for treatment of FVII deficiency can be difficult. These agents

carry a risk of thrombotic complications, particularly with repeated administration. Factor VII concentrates are purified plasma-derived preparations that have undergone a vapour-heat viral-inactivation process. If available, FVII concentrates are preferred over untreated plasma. When given at high doses, these concentrates carry a risk of thrombosis, likely because of other vitamin K-dependent factors that are present in significant concentrations. Recombinant activated FVII (rFVIIa) was originally developed to treat patients with haemophilia and inhibitors, but it can be used at lower doses for patients with congenital FVII deficiency. With increasing experience and evaluation of rFVIIa for treatment and prophylaxis in FVII deficiency, the benefits and safety profile in this setting are becoming clearer.

The decision to embark on a program of prophylaxis is determined by the patient's clinical presentation and the number of clinically significant bleeding episodes requiring intervention. Consider prophylaxis for patients with recurrent haemarthrosis or intracranial haemorrhage. Beneficial results have been reported with regimens that vary from twice daily to twice weekly treatment. Maintaining FVII levels of at least 15-25% provides adequate haemostasis levels for most surgical procedures. Preoperative FVII replacement

and monitoring of FVII levels is essential for major surgical interventions. Because of the short half-life, replacement therapy should continue postoperatively and the period of therapy is determined by the nature and extent of the procedure.

*Recombinant Factor VIIa (rFVIIa) Therapy*

Recombinant activated coagulation factor VII (rFVIIa) has been developed as a suitable way for the treatment of spontaneous and surgical bleeding in patients with congenital and acquired haemophilia with antibodies (inhibitors) against factor VIII (FVIII) and factor IX (FIX)<sup>2</sup>. In addition, it is a useful haemostatic agent proven effective in numerous other diagnostic and therapeutic procedures like biopsies in liver disease, thrombocytopenia with bleeding and heart surgery<sup>3,4,5</sup>. rFVIIa induces haemostasis at the site of injury independent of the presence of FVIII and by forming complexes with exposed tissue factor (TF)<sup>2</sup>. It bypasses activation of factor VIII and directly activates factor X into Xa and IX into IXa.

A recent interesting phase IIB randomized, double-blind, placebo-controlled, dose-ranging "proof-of-concept" trial on recombinant activated factor VII (rFVIIa) for acute intracranial haemorrhage in adult patients has been reported<sup>6</sup>. A lacking of similar experience in the paediatric population was noted. However, rFVIIa has been anecdotally reported as effective for profound bleeding episodes in children. In the paediatric literature, case reports have been made with apparent clinical improvement seen after the use of rFVIIa for acute life-threatening bleeding; however, there are limited data regarding its use in infants younger than 4 months of age, regardless of whether it is a congenital or acquired condition<sup>7</sup>.

Finally, intracerebral haemorrhage causes severe disability and a staggering economic burden. Because rFVIIa is a very expensive therapy, possible strategies for optimizing its use in these settings in the paediatric population are particularly needed. In this case we reported effective rFVIIa therapy in an inherited factor seven deficiency with acute intracranial haemorrhage. The fast improvement of haemostasis and the control of bleeding enabled the conservative approach in this patient, whereby the surgical management may increase the risk of further morbidity and mortality, when effects of vitamin K and fresh frozen plasma were of limited value.

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