

Intracranial Hemorrhage in a Neonate with Congenital Factor VII deficiency

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Abstract

Congenital factor VII deficiency is a rare autosomal-recessive bleeding disorder. Clinical manifestations vary widely from asymptomatic subjects to life-threatening hemorrhages. Treatment options include fresh frozen plasma, prothrombin complex concentrates or plasma-derived FVII concentrates. We, hereby, present a case of 9 day old male neonate, admitted with multifocal seizures, lethargy, refusal to feed, and signs of raised intracranial tension. His prothrombin time was prolonged and CT head showed acute subdural hematoma with subarachnoid hemorrhage. His clotting factor assays, done in view of spontaneous intracranial hemorrhage, showed factor VII deficiency.

Keywords: Factor VII, Intracranial Hemorrhage, Neonate.

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Introduction

Factor VII 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. Inherited factor VII deficiency is a rare autosomal recessive disorder with estimated incidence of 1/500,000 among the general population.^[1] Affected patients may remain asymptomatic for a long time or may present with bleeding manifestations. Intracranial bleeding is comparatively more common in factor VII deficiency than with other coagulation defects and they usually occur in first six months of life. Very few cases with congenital factor VII deficiency and intracranial hemorrhage have been reported. Therefore, we report such a rare case who presented with intracranial hemorrhage.

Case Report

A term male neonate, born to 2nd degree consanguineously married couple through caesarean section, with uneventful immediate postnatal life. His birth weight was 2.6 kgs. Baby presented to us on day 9 of life with multifocal seizures, vomiting and refusal to feed along with inconsolable cry. Clinical examination revealed signs of raised intracranial tension (lethargy, bulging anterior fontanel, generalized hypotonia, exaggerated DTRs, absent Moro's and sucking reflexes). His septic workup including blood and CSF culture was negative. Other investigations showed hyponatremia with normal glucose and calcium levels and adequate platelet counts. Coagulation profile showed

prolonged prothrombin time (PT) with normal activated partial thromboplastin time (aPTT). Liver function tests and d-dimer assays were normal. CT Brain showed acute subdural hematoma in occipital region with subarachnoid hemorrhage along with infarct involving posterior cerebral artery territory. Magnetic resonance arteriogram (MRV) and MR Venogram (MRV) done to rule out the arterio-venous malformations and thrombosis showed same findings as on CT scan. Supportive management was started along with vitamin K1 injections, FFP Transfusions and anticonvulsants. Although, baby had neurological improvement after 3 days; prothrombin time remained prolonged in spite of FFP transfusions. Therefore, primary coagulation disorder (clotting factor VII deficiency) was suspected in view of prolonged prothrombin time and spontaneous intracranial hemorrhage. Baby was discharged on day 26 of life with the plan of follow up to confirm the diagnosis. But the baby again brought on day 28 of life, within 48 hours of discontinuation of FFP with inconsolable cry and seizures. His PT was still prolonged (3 min) with normal aPTT. Mixing studies showed prolonged PT which could be corrected by control plasma and aged serum. Repeat CT brain showed new subdural hematoma in frontal region along with sulcal hemorrhage, ischemic changes in PCA territory. Later on, the diagnosis of coagulation disorder was confirmed by factor assays done after 72 hours of FFP discontinuation at 2 months of age, which revealed very low factor VII level (<0.01%) along with normal Factor VIII and IX assays. Baby was managed aggressively with 6 hrly FFP transfusions along with other supportive measures for one week. FFP transfusions were gradually weaned down to

every alternate day for 2 weeks and presently FFP transfusion is being given 2-3 times/week with oral anti convulsants. There was neurological improvement after 3-4 days and at present he is neurologically intact with normal milestones and no evidence of muscle weakness.

Discussion & Conclusion

Factor VII Deficiency is the most frequent among rare congenital bleeding disorders and inherited as autosomal recessive disorder, with M:F ratio of 1:1. This disorder accounts for one symptomatic individual per 500,000 population apparently without any racial and ethnic predilection.^[1] Clinical heterogeneity is the hallmark of this hemorrhagic disorder; the severity ranges from mild and asymptomatic forms to lethal ones. The correlation between FVII coagulation activity (FVII: C) and bleeding tendency appears to be poor.^[2,3] FVII deficiency is the only congenital bleeding disorder characterized by isolated prolonged prothrombin time. Clinically congenital factor VII deficiency can be divided into following categories – 1) Severe – presenting with at least one of the following symptoms: GI, CNS bleeding or haemarthrosis with or without other bleeds 2)

Moderate - have three or more symptoms with the exception of GI, CNS bleeding or haemarthrosis 3) Mild - have one or two symptoms with the exception of GI, CNS bleeding or haemarthrosis 4) Asymptomatic - detected only by investigations.^[4,5] Factor VII Deficiency is the only disorder with isolated prolonged Prothrombin time with normal activated partial thromboplastin time.^[5] Diagnosis is confirmed by doing Factor VII Assays. Prenatal diagnosis is available and should be proposed only when a family history with severe bleeding is present. Cord blood is usually obtained by either the trans-abdominal or trans-amniotic approach, and genetic analysis performed on blood samples is the gold standard method.^[6-8] Substitution therapy is the main therapeutic option of inherited FVII deficiency in severe cases and when bleeding history is present. Table 1 outlines the various treatment options available.^[9-13]

Recombinant factor VII when given at an average dose of 20µg/kg has been observed to be effective when repeatedly administered until haemostasis is achieved, but optimal treatment schedules have still not been defined.

Unlike the haemophilias, prophylaxis is not a common practice in FVII-deficient patients; it is mainly used in unweaned infants who are prone to severe and frequent bleedings. However, preliminary reports suggest that prophylaxis may also be effective in scenarios such as menorrhagia with iron deficiency and in patients with recurrent haemarthrosis.^[14] Continuous infusion of rFVIIa in surgical procedures performed in FVII-deficient patients has been reported. When properly treated, FVII deficiency is a disease with good prognosis and a life expectancy similar to that of normal individuals.

A non-replacement therapeutic approach to congenital clotting defects is a pioneering challenge in the field of blood coagulation, and treatment strategies other than gene therapy have been proposed with the aim of improving the clinical phenotype of severely FVII-deficient patients. Experimental evidence exists regarding the ability of certain aminoglycosides to suppress premature termination of translation by non-sense mutation in a number of diseases, including hemophilia B. Recently, a similar observation was reported both in cellular models and in vivo in patients with severe FVII deficiency because of non-sense mutations associated with a life-threatening bleeding tendency.^[12,13]

Table 1: Products available for FVII treatment

Products	Potency	Advantages	Disadvantages	
FFP	1	Cheap, Easily available	Volume overload	
PCC(Prothrombin)	5-10	Suitable for surgery	Risk of thrombosis	
Complex Concentrate				
PdVII (Plasma derived)	20-40	Suitable for surgery	Less effective	
rVIIa (Recombinant Factor VII)	>25000	Effective, No risk of viral transmission	Expensive, availability	Not easily

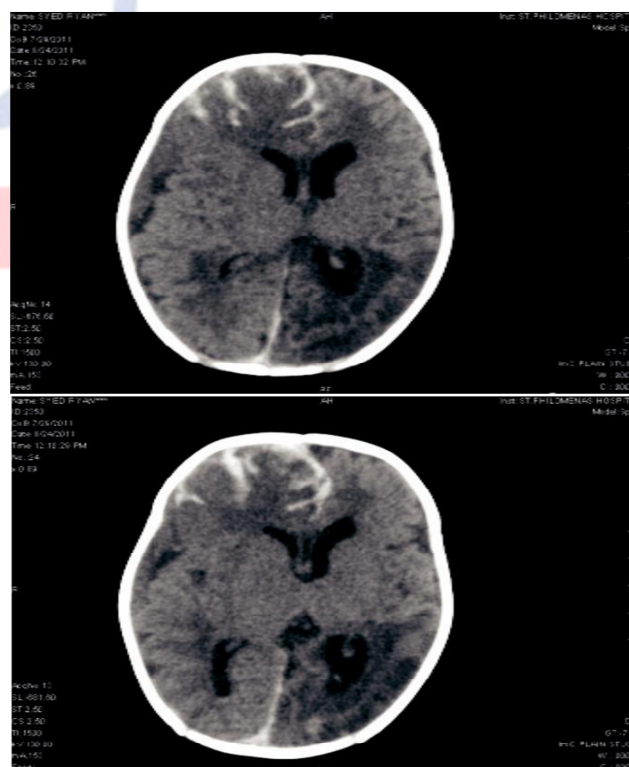


Figure 1: (CT images of Brain Showing acute subdural hematoma in occipital region with subarachnoid hemorrhage along with infarct involving posterior cerebral artery territory).

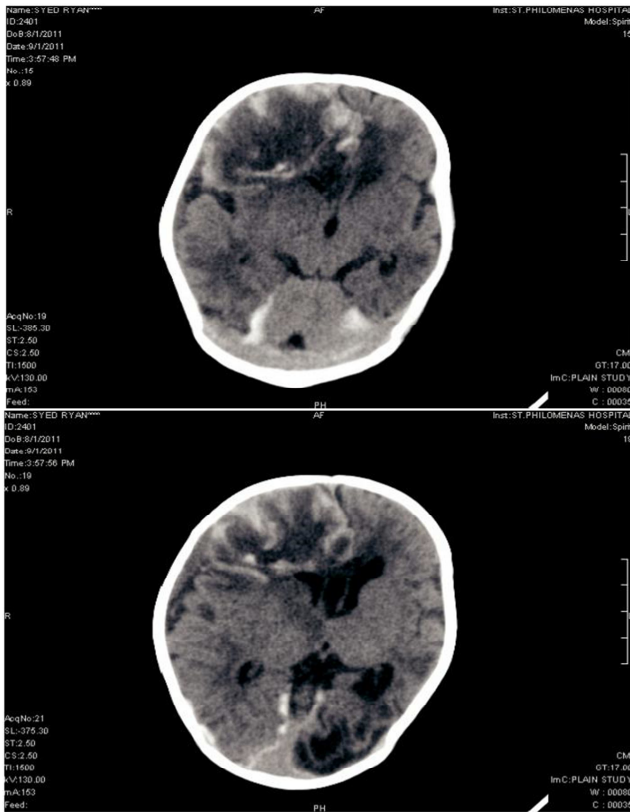


Figure 2: Repeat CT images of Brain done after 2days of discontinuation of FFP, Shows new subdural hematoma along with infarct involving posterior cerebral artery territory.

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