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Severe Recurrent Bleedings in Infant with a Factor VII Deficiency (Case Report)

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Abstract **Case Report**

Factor VII deficiency considered the most common of rare bleeding disorders. The symptoms of this affection can begin at any age, although the most severe cases are apparent in infancy. However, up to one-third of people with factor VII deficiency never have any bleeding problems. Symptoms can range from epistaxis up to cerebral hemorrhage. We here report the case of a child, diagnosed with factor VII deficiency with severe recurrent Bleedings (umbilical haemorrhage, hemarthrosis. lingual hematoma, gastrointestinal and cerebral bleeding). Prophylaxis with rFVIIa in a schedule based on 20-30 µg/kg of rFVIIa one, twice or three times a week has been described as the therapeutic regimen with the best outcomes in terms of reduction of bleeding's severity and frequency. Our patient underwent early prophylaxis with a 30 µg/kg of rFVIIa a week schedule. Unfortunately, prophylaxis hasen't been successful to prevent further bleedings. The evolution was marked by occurrence of several gastrointestinal and cerebral bleeding, then death by a cerebral hemorrhage at the age of 6 months. Congenital Factor VII deficiency is a rare cause of bleeding disorder, which should be suspected in a healthy bleeding child presenting in infancy when platelets and aPTT is normal with a deranged PT.

Keywords: Bleeding, Factor VII, Symptoms, umbilical haemorrhage, lingual hematoma.

INTRODUCTION

Factor VII deficiency (Also known as Alexander's disease) was first recognized in 1951. Considered the most common of rare bleeding disorders. its incidence is estimated at 1 per 300,000-500,000 [1]. It is caused by mutations of the *F7* gene and is inherited as an autosomal recessive disorder [2].

he signs and symptoms of this affection can begin at any age, although the most severe cases are apparent in infancy. However, up to one-third of people with factor VII deficiency never have any bleeding problems. Symptoms can range from epistaxis up to cerebral hemorrhage [1, 2]. We here report the case of a child, diagnosed with factor VII deficiency with severe recurrent Bleedings

OBSERVATIONS

We report the case of a 29-day-old male infant, born from non-consanguineous parents after physiological delivery. He had a remarkable family history: sister died on day of life 7(DOL), by umbilical haemorrhage. He was born in hospital and had received intramuscular vitamin K prophylaxis. No other drugs were administered. During the DOL4, he presented umbilical haemorrhage, Upon transfer to a level III Medical Center on the same day. Physical examination revealed a pale appearance and vital signs were unremarkable.

Initial blood tests revealed anemia (hemoglobin, 10 g/dl), platelet count, hepatic function, and C-reactive protein (CRP) were normal, remarkable coagulopathy with isolated prolonged prothrombin time (PT: 5%), activated partial thromboplastin time (aPTT) and fibrinogen were normal. Coagulation factors were therefore checked, with the only evidence of severe FVII coagulation activity deficiency (1,6%; normal range >50%). Transfontanellar and abdominal ultrasounds were unremarkable. The patient was transfused with packed RBC and fresh frozen plasma, with good evolution. In the following days several other hemorrhagic episodes occurred. At first he experienced spontaneous non-traumatic hemarthrosis. Later, appearance important lingual hematoma with pale appearance at DOL 29. Lingual hematoma and

hemarthrosis were successfully treated with a therapeutic dose of recombinant activated FVII (30 µg/kg/6h). A prophylactic treatment at a dosage of 30 µg/kg/week was started [2].

Figure 1: Lingual hematoma observed at our patient

Figure 2: Ankle hemarthrosis observed at our patient

However, at the age of 3 months, the child presented with an unquantified fever, food vomiting and mucous diarrhoea. Physical examination revealed a pale infant, hypotonic, febrile at 38.4 with bulging anterior fontanel. A subsequent CT scan revealed a subacute left hemispheric subdural hematoma.

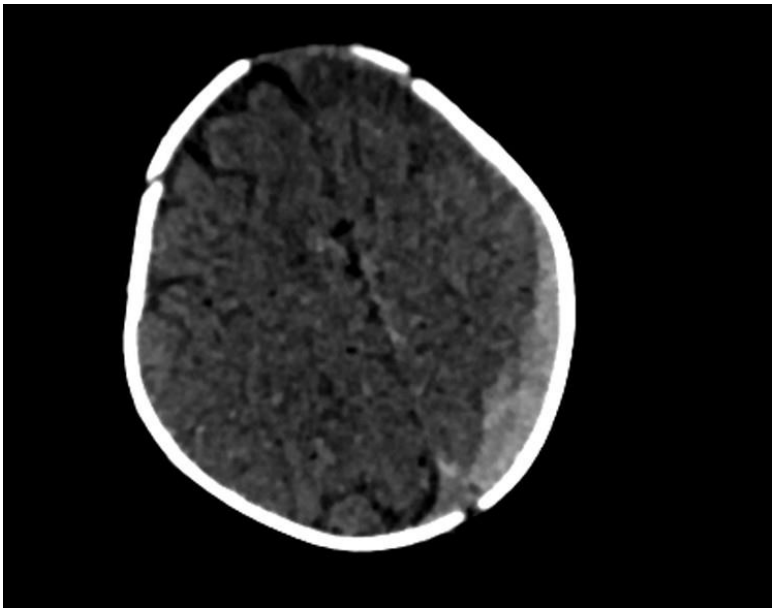

Figure 3: left parieto-occipital acute subdural hematoma.

The patient was transfused and treated with a therapeutic dose of recombinant activated FVII (60 µg/kg/6h). The evolution was marked by occurrence of several gastrointestinal and cerebral bleeding, then death by a cerebral hemorrhage (right frontotemporal intraparenchymal hematoma) at the age of 6 months.

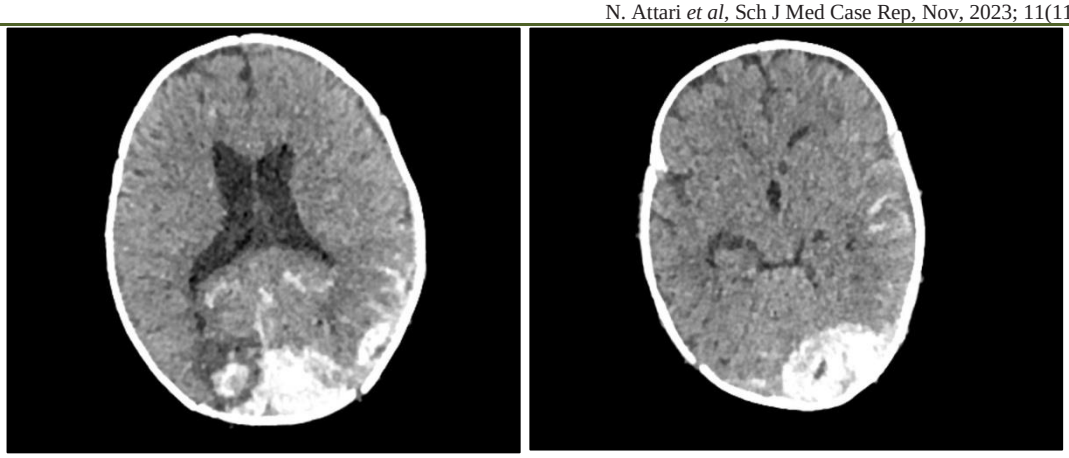

Figure 4 : Right occipital intraparenchymal hematomas and left extradural hematoma at the age of 4 months

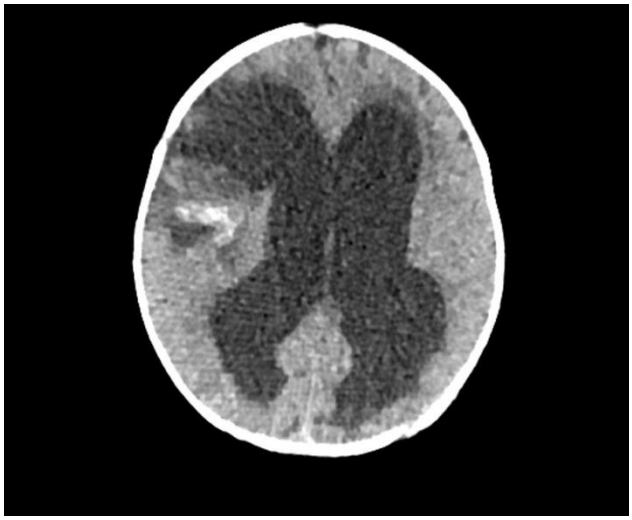

Figure 5 : Right frontotemporal intraparenchymal hematoma with subarachnoid hemorrhage and quadriventricular dilatation at the age of 6 months

DISCUSSION

We described a challenging case of recurrent neonatal hemorrhages caused by factor VII deficiency. Congenital factor VII deficiency is a rare autosomal recessive bleeding disorder, accounting for one symptomatic individual per 500,000 [3, 4]. Frequency is higher in countries where consanguineous marriage is more common, as in the case of Morocco [4]. This inherited coagulation disorder is the only congenital bleeding disorder characterized by isolated prolonged prothrombin time, as observed in our case. Clinical heterogeneity is the hallmark of this hemorrhagic disorder, patients can be asymptomatic or experience different types of bleeding, with the most frequent being epistaxis, gum bleedings, menorrhagia, ecchymoses, and hematomas. Hemarthrosis and cerebral and gastrointestinal hemorrhages can also occur [4, 5].

FVII deficiency showed a poor association between coagulant activity level and bleeding severity [6], the classification of FVII deficiency is usually based on clinical features. Age of onset is a crucial element, being a significant predictor of severe disease [7]. Considering the occurrence of early onset, multifocal major bleedings and the extremely low FVII:C, our patient was classified as a severe case.

Mutations of the FVII gene have been characterized in the vast majority of FVII-deficient patients. Mutations are very heterogeneous, and missense changes are the most frequent lesions (70 to 80%) [8]. Homozygous and compound heterozygous patients experience the most severe forms of the disease and carry a significant risk of premature death [7]. Genetic investigation in our patient is ongoing.

Management of factor VII deficiency bleeding disorder, in terms of substitution therapy and therapy schedules, is not yet optimal [4]. Factor VII level alone cannot drive management because it cannot predict bleeding risk tendency Several different products can be used for FVII replacement depending on availability, including fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), plasma-derived FVII concentrates, and recombinant FVIIa [9]. Recombinant FVIIa is considered as the first-line therapy and the most frequently used.

Replacement options are characterized by peculiar features. Recombinant activated factor VII stands out due to the advantage of efficacy and has no risk of transmitting pathogens, while the disadvantages might be the higher cost per dose [10]. Plasma-derived factor VII is also an effective choice at a lower price, while other vitamin K-dependent factor concentrations lead to higher prothrombin levels and may be associated with thrombosis, which remains a suitable option for replacement therapy [9, 10]. According to recent reports, the recommended dose per injection is 15–30 μg/kg. In mild/moderate bleeds or after a minor surgical procedure, a single dose of recombinant FVIIa is often adequate for treatment. For severe bleeding or for major surgery, dosing can be repeated every 4–6hours until hemostasis is achieved; the dose and frequency should be individualized to the patient [9].

Long-term prophylaxis should be considered and started soon after the first clinically significant bleeding in severe forms of FVII deficiency as is the case of our patient [10], Short-term or intermittent prophylactic schedules can also be considered, particularly in conditions like menorrhagia or severe hemarthroses [11].

Prophylaxis with rFVIIa in a schedule based on 20-30 μg/kg of rFVIIa one, twice or three times a week has been described as the therapeutic regimen with the best outcomes in terms of reduction of bleeding's severity and frequency [10]. Our patient underwent early prophylaxis with a 30 μg/kg of rFVIIa a week schedule. Unfortunately, prophylaxis hasen't been successful to prevent further bleedings.

CONCLUSION

Congenital Factor VII deficiency is a rare cause of bleeding disorder, which should be suspected in a healthy bleeding child presenting in infancy when platelets and aPTT is normal with a deranged PT.

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