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A Neonate with Acquired Factor VII Deficiency Successfully Managed with Immunomodulatory Therapy

Nof Saadi Alqarni [a, b], Ali H. Algiraigri [a, b, *]

[a] Hematology Department, King Abdulaziz University Hospital, Jeddah, Saudi Arabia
[b] Oncology Department, King Faisal Special Hospital and Research Center, Jeddah, Saudi Arabia

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ABSTRACT

Acquired factor VII deficiency secondary to circulating inhibitors is rare in children but is a potentially life-threatening condition. Such a disease is challenging to diagnose and often difficult to manage. Here, we report on a newborn that presented with a catastrophic intracranial hemorrhage who failed to respond to conventional supportive measures including multiple doses of fresh frozen plasma and factor VII replacement; however, he had a complete correction of prothrombin time 8 h after immunomodulatory therapies in the form of steroid and intravenous immunoglobulin. Such measures helped stabilize his bleeding and allowed urgent neurosurgical intervention.

1. Introduction

Hemostasis is a normal physiological process that aims to prevent and stop bleeding at the site of blood vessel injury [1]. Such a process is accomplished by several tightly regulated proteins called coagulation factors. The absence or dysfunction of such factors is associated with abnormal bleeding or clotting. Factor VII is one of the essential coagulation factors that prevent bleeding [1]. The deficiency of factor VII is associated with abnormal bleeding. Bleeding symptoms can range from mild skin and mucous membrane bleeding to life-threatening bleeding [2].

Hereditary and acquired factor VII deficiency have been reported in the literature. Congenital factor VII deficiency is an autosomal recessive bleeding disorder that was initially described by Alexander et al., in 1951 [2,3]. It is a rare disease with a prevalence of 1 per half a million. Acquired factor VII deficiency is likewise rare and can be due to decreased production (related to vitamin K deficiency) or result from antibodies against factor VII (inhibitors) [2,3]. Several causes have been identified for such deficiencies of factor VII including liver disease, malabsorption, infections, autoimmune diseases, malignancies, and medications.

Abnormal bleeding is the hallmark presentation of factor VII deviancy regardless of the underlying etiology. Such bleeding can be induced by injury or occur spontaneously without apparent cause. Although not an optimum correlation, bleeding severity tends to correlate with factor VII level [2,3]. Bleeding can range from mild skin bleeding to severe life-threatening bleeding. Here, we report the rare phenomenon of acquired factor VII deficiency secondary to inhibitors with challenging clinical presentation in a newborn.

2. Case presentation

A full-term 20-day-old male neonate who had been born at home presented with a history of decreased activity, jaundice, and an increase in head size for 2 days. There was no history of trauma nor vomiting according to the family. The family reported on and off fever and poor feeding. He was found to be febrile and jaundiced and had a tense anterior fontanelle, sluggish pupil reaction, and minimal limb movements that were bilaterally unremarkable. The case was admitted and managed initially as neonatal sepsis for investigation. His initial pertinent laboratory investigations are presented in Table 1.

Besides supportive care and antibiotics, the patient received Vitamin K, blood, cryoprecipitate, and fresh frozen plasma (FFP). Urgent CT brain revealed a massive intracranial hemorrhage (ICH) with midline shift as depicted in Fig. 1.

Neurosurgical intervention for the ICH was planned; however, it

* Corresponding author. King Abdulaziz University Hospital, Hematology Department, Jeddah, SA, 22252, Saudi Arabia.
E-mail address: aalgiraigri@kau.edu.sa (A.H. Algiraigri).

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Table 1
Laboratory workup

Laboratory results	Patient results	Reference results
WBC	25 K/ul	9–37 K/ul
Hb	3 g/dl	16.5–21.5 g/dl
MCV	131 fL	95-125 fL
Platelets	254 K/ul	150–450 K/ul
Fibrinogen	177 mg/dl	200–393 mg/dl
Coagulation profile	Prothrombin time (PT) > 2 min	9.4–12.5 sec
	Activated partial thromboplastin time (APTT) 58	25.1–36.5 sec
	INR>10	0.85–1.3 ration
Mixing study	PT > 2min	Negative
Factor assay	FVII 2%	50–120%
Blood culture	Coagulase-negative staphylococcus	
Family study	Normal PT and PTT	
	Normal FVII levels	

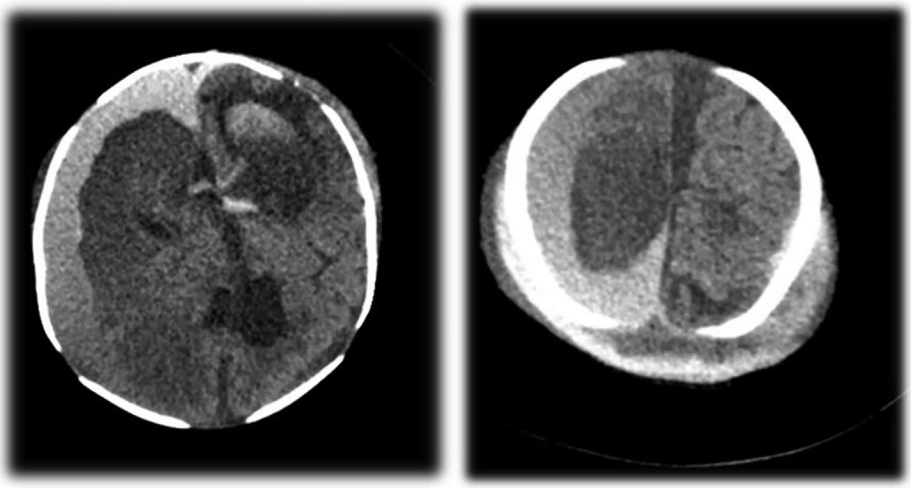

Fig. 1. Axial CT demonstrates a marked right subdural hematoma with midline shift, interventricular hemorrhage in the posterior horn of the lateral ventricle, and small subarachnoid hemorrhage.

was determined to be infeasible due to persistently high isolated PT despite initial management with vitamin K, cryoprecipitate, and FFP. Factor VII level was sent initially, but no results were available that night. Two empirical doses of factor VII were given, but PT remained high (>2 minutes). Initially, hemorrhagic disease of the newborn was considered, but it did not fully explain the case. Factor VII deficiency secondary to inhibitors was possible due to the failure of correction in the mixing study and post Factor VII replacement. As such, a trial of intravenous immunoglobulin (IVIG) 1 gm/kg ×1 and methylprednisone 1mg/kg/dose q6 hourly for 48 hours was given and was then tapered over 5 days. Eight hours later, a complete correction of PT was observed, which allowed the patient to undergo an urgent neurosurgical intervention (hematoma evacuation and insertion of a drain). There was no significant intraoperative or postoperative bleeding. The patient was closely monitored in the pediatric intensive care unit (PICU), where his PT has repeatedly remained normal. On day 3 of this PICU stay, the patient developed a line related clot (femoral vein) which was managed conservatively without anticoagulation due to the concurrent ICH.

3. Discussion

Although there are many known causes of acquired FVII deficiency like vitamin K deficiency or malabsorption, warfarin, and liver disease, little is known about acquired FVII deficiency secondary inhibitors [2,3]. The exact incidence of such disease is unknown and is thought to be rare due to the limited reported cases. However, the true incidence might be underestimated. To date, only four case reports of children with factor VII deficiency secondary to inhibitors have been described, and none of them were reported in the neonatal age group, making our report the first one [3].

In the absence of previous exposure to factor VII, inhibitors to factor VII are extremely rare and are likely related to infections, inflammatory process, malignancies, or bone marrow transplantation [3]. Diagnosis of such a rare disease requires a high index of suspicion for an accurate diagnosis. The initial clue to such a condition can be derived from an initial coagulation profile that indicates isolated prolongation of PT that fails to correct after the mixing study, as in our case. A confirmatory assessment of factor VII level must be performed, which will typically be low or completely absent. Although the factor VII inhibitor assay may be used as a confirmatory step, it is usually not readily available in most labs. The decision to diagnose and manage factor VII with inhibitors relies on the initial historical data (like bleeding history, previous exposure to factors, and/or infection or inflammatory processes) as well as the initial coagulation profile (PT, aPTT, mixing study, and factor assay). The first clue for circulating inhibitors to factor VII is the failure to correct PT in the mixing study. As a rule of thumb, correction of PT or APTT in mixing study indicates a deficient state, while failing to correct indicates the presence of antibodies. The

presence of inhibitor(s) is an indication of the urgent need to call for the hematology service to help diagnosing and managing such cases.

The clinical presentations of acquired factor VII inhibitors can vary from a mild bleeding phenotype to severe life-threatening events [3]. The first step in the management of acquired FVII inhibitors is to decide whether such phenomena are related to previous exposure to FVII or to de novo inhibitor formation. Due to the rarity of such conditions and life-threatening events, the majority of patients receive FFP with vitamin K or FVII concentrate (regular or higher doses) to overcome such inhibitors. If there is no improvement, immunomodulatory agents have been used, including IVIG, steroids, cyclophosphamide, and plasma exchange [3]. [-5] The expected response of FVII inhibitors has been reported to be similar to other acquired inhibitors [4,5]. In our case, due to the age of the child and severe life-threatening ICH, we elected to use both IVIG (1g/kg) and methylprednisone (1mg/kg q6), which led to a complete correction of PT after 6–8 hours.

To our knowledge, this is the first reported case of a neonate with acquired FVII deficiency due to inhibitors. We cannot emphasize enough that a mixing study is a critical diagnostic step that should be performed in cases with prolonged coagulation profiles. Despite his life-threatening bleeds, the newborn responded well to the combination of IVIG and steroid.

Authors' contributions

All authors contributed to this case management and report writing.

Funding

No funding was received for this study.

Consent

A consent form was obtained and signed by the patient and kept in her medical records.

3.1. Ethical statement

Hereby, I/Ali Algiraigri/consciously assure that for the manuscript/A Neonate with Acquired Factor VII Deficiency Successfully Managed with Immunomodulatory Therapy/the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text are indicated as such by using quotation marks and giving proper reference.
7) All authors have been personally and actively involved in substantial work leading to the paper and will take public responsibility for its content.

Declaration of competing interest

The authors declare no conflicts of interest.

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