INHIBITOR DEVELOPMENT IN CONGENITAL FACTOR VII DEFICIENCY – CASE PRESENTATION

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ABSTRACT

Congenital factor VII deficiency is a rare disease. Inhibitor development in congenital factor VII deficiency is an extreme rare phenomen, as the main challenge of replacement therapy by a high rate of life-threatening bleeding, that renders replacemrnt therapy less effective. Due to the important of the issue, we would like to present this case-report, It was a female 11 months with congenital factor VII deficiency experiencing recurrent epistaxis, hematoma, intracranien hemorrhages from second month of life, and successful treatment by double dose of recombinant activated VII. Some conclusions are that, inhibitor detection in congenital factor VII deficiency with severe recurrent hemorrhage or less successful of replacement therapy is always needed; and high dose of rFVIIa in treatment of congenital factor VII deficiency can successfully stop bleeding.

Key words: *Factor VII deficiency, Factor VII Inhibitor, Replacement therapy.*

1. INTRODUCTION

Factor VII (FVII) is a coagulation factor in the exogenous thrombin cycle, is produced from the liver and circulates in plasma in two forms, mostly in the form of an inactive single chain. Factor VII is activated into VIIa in the presence of promoter, activated Factor VII (FVIIa) binds to promoter in the presence of Ca++ activating factor IX into IXa, and factor X into Xa to convert prothrombin to thrombin. Factor VII deficiency causes prolonged prothrombime (PT) time [1]. Congenital factor VII deficiency disease is a rare hemorrhage disease with inherited recessive gene on chromosome 13, usually found in homozygous form, due to manifestations of severe haemorrhage in the skin, mucous membranes, quitecommon intracerebral hemorrhage and postoperative bleeding [2]. The therapy for congenital factor VII deficiency is replacement therapy with prothrombin complex concentrate (PCC), fresh frozen plasma (FFP) and plasma-derived FVII - pd-FVII and recombinant activated Factor VII - (rFVIIa) [3]. In the course of replacement therapy, FVII inhibitor development can occur, causing life-threatening serious bleeding and reducing effectiveness of treatment [4], which is a challenge in the treatment of congenital factor VII deficiency [5]. In this article, we would like to introduce a case of congenital factor VII deficiency with inhibitor development thatwas saved at the Vietnam National Children's Hospital; therebywewould like to review some issues through the medical literature and discuss

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the diagnosis and treatment of congenital FVII deficiency with inhibitor development.

2. CASE PRESENTATION

Pediatric patient Le Thi P., 11 months old, was hospitalized because of bleeding, bruising around the eye socket, bleeding in the tooth root, in the oral cavity and black stools. The patient was diagnosed with congenital factor VII deficiency from 2 months of age because of showing sign of hemorrhage, the test showed prolonged prothrombin time (PT 96.2 seconds), APTT 36.2 seconds, prothrombin rate of 7%, Fibrinogen 1.67g/L, ineffectivevitamin K treatment. Examination of clotting factors showed that factor VII (FVII) was 0.6%, FII 66.9%, FV 81.8%, FIX 36.4%, FX 77.6%. At 3 months of age, the patient suffered from cerebral hemorrhage and was treated at the Vietnam National Children's Hospital many times with FVIIrich product.

This time, she was hospitalized because of hematoma in the eye socket, bleeding intooth root, oral cavity, black stools, the patient was treated with NovoSeven (recombinant activated factor VII - rFVIIa), fresh plasma. After 12 days of treatment, the hemorrhage condition decreased, but the patient fell, showed signs of intracranial hemorrhage such as lethargy, left hemiplegia, 2mm bilateral pupils, light reflexes, blue skin, pale mucosa with scattered hemorrhages under the skin. The patient underwent a CT scan with a diagnosis of cerebral hemorrhage in the right parietal region. The patient was intubated for mechanical ventilation, continued to be treated withNovoSeven 30 mcg/kg/time x 6 times/day. Then check again, it was shown that PT still lasted 65.5s, prothrombin rate decreased, only 11%, for Nijmegen-Bethesda technical tape inhibitor test, FVII inhibitor was 24BU. The patient continued to be treated with NovoSeven, double dose, 60mcg/kg/time for 5 days, after checking again, PT was shortened to only 10.4 seconds, Prothrombin rate increased to 107%. Next, the patient was treated for 4 more days with the same dose of 30 µg/kg/time × 6 times/day for 4 days, PT after 14.7s injection (prothrombin rate of 66%). Finally, after 9 days of rFVIIa-based treatment, the patient was released from machine, subject to hemostasis, recorded a stable condition and was discharged from hospital after 3 more days.

3. DISCUSSION

Congenital factor VIIdeficiency or proconvertin deficiency disease is a rare disease, estimated at 1 in 500,000 people, regardless of ethnic group or geography [6]. Compared with the frequency of other rare coagulation deficiency diseases such as deficiency of fibrinogen, prothrombin (FII), factor V, deficiency of factors V and VIII, X, XI, XIII, the frequency varies from 1/5,000,000 to 1/2,000,000 [3]. FVII deficiency is an autosomal recessive genetic disease that is more common in societies with a high rate of consanguineous marriage. The disease is usually diagnosed in the homozygous form, when there are clinicalhemorrhage manifestations. Heterozygous form usually does not show hemorrhage manifestations, prothrombin time is normal, so it can only be detected when specifically testing FVII in people in the family of patients with congenital FVII deficiency. Based on FVII activity, FVII deficiency is classified into 3 levels - mild when FVII activity is >20%, moderate 10-20% and severe <10%. Clinical manifestations of FVII deficiency are skin and mucosal bleeding, nose bleeding, gastrointestinal bleeding, hematoma, intracranial bleeding and postoperative bleeding.

Congenital FVII deficiency with inhibitor development is a very rare disease. In the study of Sham M et al., 2019 in 50 patients with congenital FVII deficiency in Iran, only 2 patients developed inhibitors, the rate was only 4% of people with congenital FVII deficiency [6]. Recent synthetic study by Ramazampour N. et al. in 2021, it was found that, from 1990-2020, only 13 published studies were collected in the world, among 380

patients with congenital FVII deficiency, only 27 patients developed inhibitors, the rate of congenital FVII deficiency was 7.1%. All of the patients who developed an inhibitor were in case of severe congenital FVII deficiency (FVII <10%), previously received replacement therapy, 37% (10/27) with rFVIIa, 7% (2/27) with FFP, 4% (1/27) with pd-FVII, 37% (10/27) combining rFVIIa with FFP, 11% (3/27) rFVIIa with pd-VII and 4% (1/27) having a combination of 3 preparations. Age of inhibitor detection in congenital FVII deficiency was mostly before 5 years of age (73%). Over 90% of cases had high inhibitory concentrations (> 5BU) [7].

In nature, FVII inhibitors are alloantibodies, polyclonal immune responses, antibodies belonging to IgG group, more dominant than IgG1 subclass, less so than to IgG4 subclass [7].

Basically, FVIIinhibitor molecularis genetic mutation, 40% of patients have missense mutations, 30% nonsense mutations, 20% mutations of deletion c9711 on exon 7, and 10%mutations of missense double and single deletion. These genetic properties play an important role in the development of the FVII deficiency inhibitor [7]. Study in hemophilia A showed that genetic changes played an important role in inhibitor formation [8].

Regarding clinical manifestations, FVII deficiency is mucosal bleeding, nose bleeding, gastrointestinal bleeding, joint hematoma, intracranial bleeding, postoperative bleeding [9]. During the replacement therapy of congenital FVII deficiency, multiple anti-FVII heteroantibody inhibitors maydevelop, which is an important challenge. Patients with congenital FVII deficiency with inhibitor will at increased risk of more severe disease, life-threatening bleeding. The critical clinical manifestation of FVII deficiency is intracranial bleeding, many studies showed that intracranial bleeding when the inhibitor occurs increased to 10%, heavy bleeding such as large hematoma, joint hematoma, gastrointestinal bleeding was also more common [7,1]. Thus, the development of coagulation factor inhibitors increases the rate of serious illness and death, many complications, increases costs, increases the mental burden on the family and society and poses great challenges in terms of treatment.

Regarding diagnostic practice - Through the medical literature, as well as through this patient, an experience is that in the treatment of coagulation factor deficiency by a replacement therapy, attention must always be paid to the development of inhibitors. When the treatment of FVII deficiency disease with a replacement therapy fails to make clinical progress well or the disease progresses more seriously and there is a devleopment of inhibitors, it is necessary to test for finding FVII inhibitors to confirm the diagnosis. FVII inhibitors can be quantified by the Nijmegen-Bethesda test, when inhibitor concentration> 5BU may confirm the diagnosis. For the patient referred above, the FVII inhibitor concentration was 24BU.

Handling of congenital FVII deficiency with inhibitor development is not an easy process. The main objective of treatment is to stop bleeding and remove the inhibitor [6]. According to some reports, high dose or repeated dose administration of rFVIIa (NovoSevens) may or may not be effective [10,11,12]. Research on the treatment of FVII deficiency with inhibitors has still been limited. Synthesizing 13 studies from 1990 to 2020 in the world, Ramenzapour N. et al. (2021) recruited 27 patients with FVIIdeficiency with inhibitors, 12/27 (44%) of rFVIIa-treated patients showed positive results and 3/27 treated with high-dose rFVIIa or FEIBA (Factor Eight Inhibitor Bypassing Activity) died from recurrent intracranial bleeding. 1/27 did not respond to rFVIIa, treated further with 80-100 IU/kg of FEIBA showed good clinical response, may control inhibitors, and 1/27 received Immune Tolerance Induction (ITI) therapy, successfully concentrated pd-FVII [7]. The patient referred above was

treated with double high dose rFVIIacompared to previous therapy succeeded, stopped bleeding andand clinically stable.

4. CONCLUSION

- Development of inhibitors in patients with congenital FVII deficiency is rare, but is serious life-threatening condition, a great challenge for treatment.

- It should be noted that the development of inhibitors is detected during replacement therapy for patients with FVII deficiency.

- Treatment of congenital FVII deficiency with inhibitor development with high dose rFVIIa helps stop bleeding, savelife of patients.

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