Original Article

Prothrombin (Factor II) deficiency as a rare bleeding disorder

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ABSTRACT

Prothrombin or factor II is an important factor in the coagulation cascade and a part of the common pathway. Deficiency of prothrombin (factor II) can be either inherited or acquired. The inherited Prothrombin deficiency is considered as one of the rarest bleeding disorders. It is inherited as autosomal recessive. This study reports a young girl at Saudi German Hospital in Al-Madinah, KSA with a prolonged PT, aPTT, the nose and gum bleeding with a very low level of factor II.

Keywords: Prothrombin deficiency, factor II deficiency, rare bleeding disorders, rare coagulation factors deficiency.

Introduction

Hemostasis is a complex mechanism that depends on three major steps as described by Virchow. One of these steps is coagulation which includes proteins, Factors I, II, V, VIII, IX, X, XI, XII and XIII which are synthesized in the liver and are triggered in the coagulation cascade (Table 1, Figure 1) [1]. Prothrombin is a 72-kDa, vitamin K-dependent glycoprotein, which has a plasma concentration of approximately 100 µg/mL [1, 2]. Factor II (Prothrombin) is required in the common pathway of the coagulation cascade. Prothrombin deficiency can be acquired or inherited. The acquired prothrombin deficiency occurs in patients with vitamin K deficiency, liver disease, patients on warfarin, or in the presence of inhibitors in patients with lupus anticoagulant hypoprothrombinemia syndrome [3, 4]. The inherited prothrombin deficiency is of the rarest coagulation factor disorders [5].

Case report:

An 11-year-old girl, originally from Afghanistan admitted at Saudi German Hospital in Al-Madinah; KSA because of an activated partial thromboplastin time (aPTT) and prolonged prothrombin time (PT). She had on and off bleeding from the gum and nose, had not gone through a surgical procedure, had no joint pain or swelling, had a very low activity at home, and her parents were cousins. The initial workup was done for factors, affecting both aPTT and PT, including fibrinogen as well as factor II, V, and X. The laboratory results showed a very low level of factor II (9%) with the normal levels of factors V and X (92%, 7.06 g/L, and 89%) respectively. The repeated test of factor II confirmed its very low level (6%). The mixing study showed the complete correction of her coagulation profile with no inhibitors. She had iron deficiency anemia secondary to the recurrent bleeding. Her treatment was started with 15 ml/kg of FFP transfusion which was later increased to 25 ml/kg. She had pre and post-transfusion factor II assay (Table 2) with the aim of the factor II level above 25%. Her factor II level was again below 10%, 4 days after transfusion. She required FFP transfusion almost every 3-4 weeks as well as a regular Tranexamic acid, 500mg twice daily. On the subsequent visit, she had left ankle swelling which was confirmed by MRI, which was resolved after receiving FFP. Despite a very low level of factor II, she had no major bleeding. She had not started menstruating yet.

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Discussion

Prothrombin deficiency can be acquired or inherited. Quick first explained the inherited prothrombin deficiency in 1947 and further described in 1955 and 1962 [1]. It is considered as one of the rarest inherited bleeding disorders which one in two million people suffers from it [2]. Few case reports have been

reported mainly in Caucasus and Iran. The inherited type of this disorder is autosomal recessive and the acquired type occurs in patients with liver diseases, deficiency of vitamin K, on oral warfarin or very rarely in patients with lupus anticoagulant [1-4].

Prothrombin gene with the molecular weight of 21 kb, located on chromosome 11 (11p11). The hemostatic level of prothrombin is approximately between twenty and forty percent with a half-life of about 3 days [5].

Thrombin is the active form of prothrombin, which has positive feedback on different steps of the coagulation cascade. It is responsible for converting fibrinogen to the active form, fibrin, in the presence of the active form of factor XIII for a stable clot. Thrombin has also negative feedback on this coagulation cascade through binding to thrombomodulin (TM) and activation of the protein C pathway to prevent further clot formation and extension [6, 7].

There are 2 main types of prothrombin deficiency. Type I or hypoprothrombinemia (reduction of antigen level as well as activity) and type II or dysprothrombinemia, which is associated with the reduction of enzymatic activity but normal antigen level [2]. The disease is detected by prolonged PT and aPTT and definitely diagnosed by the factor assay. Patients, suffering from the inherited disease severe hypoprothrombinemia usually present early in life, while the milder form may be presented later at any age [5]. Presentation varies based on the factor II level. Severity is classified into severe, moderate and mild based on the factor II (Prothrombin) level as in hemophilia A or B but others consider undetectable level as severe while level equal or below 10% is moderate [5]. (Table 3) Mild cases are associated with mucosal bleeding. Severe life-threatening hemorrhage, including intracranial hemorrhage, is found in neonates with severe prothrombin deficiency [4]. A complete prothrombin deficiency is not compatible with life [8]. In both acquired and inherited hypoprothrombinemia, the morbidity and mortality risks are related to the circulating level of factor II [2]. Prophylactic treatment is suggested in children with a severe prothrombin deficiency (levels less than 2%) with life-threatening bleeds [7, 8].

Since 1947, no progression has occurred in the development of factor II concentrates as there are few cases reported till now. The development in this way is very slow probably because of the cost-benefit reasons especially with current financial limitations as well as the rarity of cases worldwide. There are neither clear guidelines on prophylaxis nor on treatment. Treatment includes prothrombin complex concentrates (PCC) or fresh frozen plasma (FFP) [9-12]. Prophylaxis transfusion is to prevent bleeding episodes while treatment is to manage acute bleeding. Taking into consideration the short half-life of prothrombin (approximately 3 days), FFP may be required on weekly bases [10-12]. If 4-6 units of FFP are required per transfusion that means the patient will require 312 units of FFP per year. This does not count for the number of units required during acute bleeding episodes or surgery. This may not be practical. Treating acute bleeding episodes with FFP at 20-15 ml/kg usually raises the level of factor by 25%. During surgical procedures or more severe bleeding episodes, a higher dose of FFP or more frequent doses may be required. Another option is PCC at the dose of 30-20 IU/kg based on factor IX units in the product used [9, 10]. Anti-fibrinolytic therapies such as Tranexamic acid can be administered intravenously or orally to treat mucosal bleeding. Anti-fibrinolytic may be the treatment of mild to moderate bleeding episodes [1, 2, 5]. Hormonal therapy with estrogens and/or progesterone may help to reduce menstrual blood loss in patients with menorrhagia [9, 10, 13, 14]. In this report, the patient was given FFP initially because she had an active nose and gum bleeding. Later on, it was decided to transfuse her based on the clinical symptoms, coagulation profile, and factor II level. Her socioeconomic status had also taken into consideration. She required FFP almost every 4-6 weeks because of recurrent nose and gum bleeding despite being on regular Tranexamic acid 500mg twice daily. This might be the first inherited prothrombin deficiency case to be reported in KSA.

Such patients with factor II deficiency need a novel treatment as recombinant factor II to improve their quality of life.

Conclusion

Prothrombin (Factor II) deficiency either acquired or inherited is of the rarest bleeding disorders. The available treatment is neither specific nor optimistic. Current treatment guidelines are based on personal experience or expert recommendations. Recombinant factor II concentrate is not available up to now. Future manufacture of such factor may change the quality of life of such patients.

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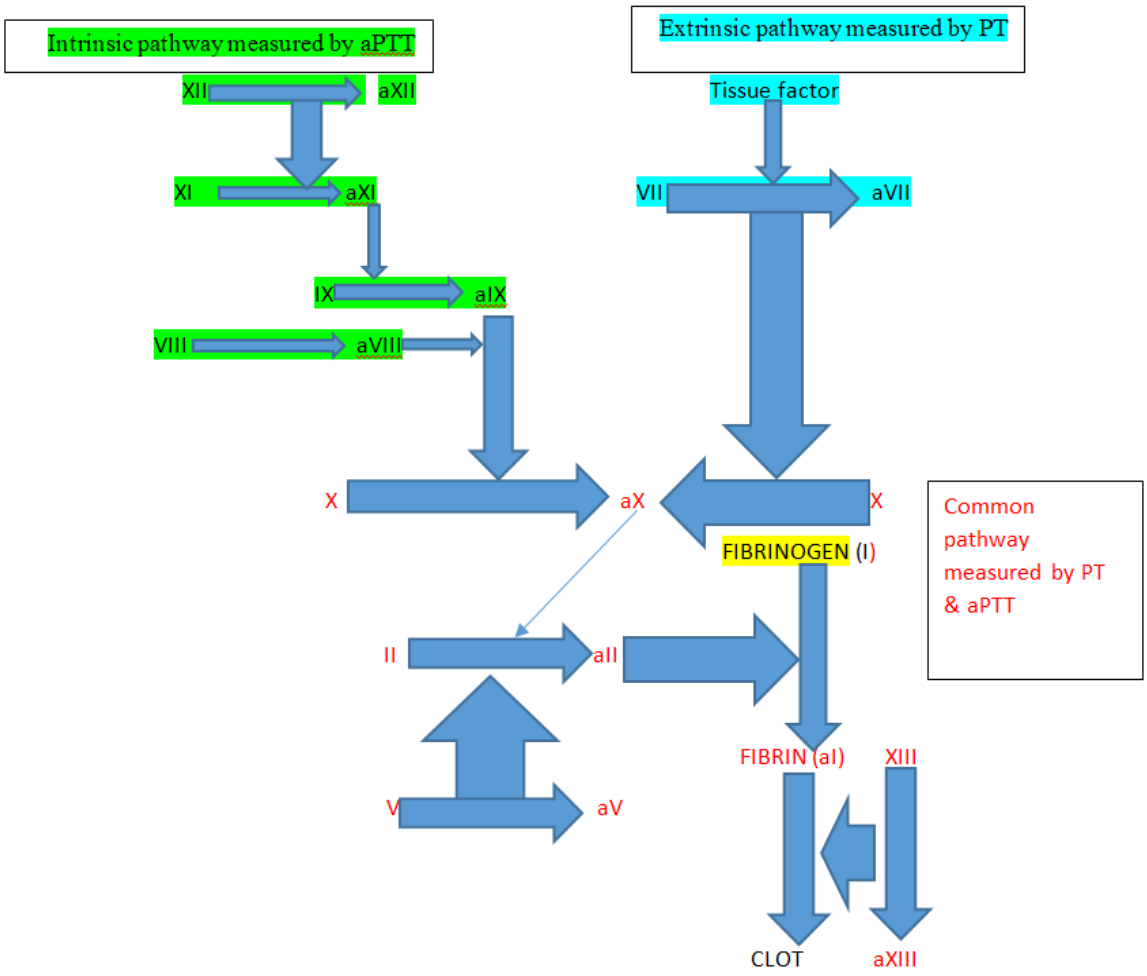

Figure 1: Coagulation Cascade Pathways

Table 1: List of Coagulation Factors

Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III, Tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin, labile factor
Factor VII	Proconvertin, stable factor
Factor VIII	Antihemophilic factor
Factor IX	Christmas factor
Factor X	Stuart factor; Stuart-Prower
Factor XI	Plasma thromboplastin antecedent
Factor XII	Hageman factor
Factor XIII	Fibrin stabilizing factor
Prekallikrein	Fletcher factor
Hmwk	Fitzgerald factor

Table 2: Coagulation profile and factor II level Pre and Post FFP transfusion

Timing	Factor II Level	PT	INR	aPTT	Comments
Initial (at diagnosis)	9 % (6%)	28.2 second	2.17	> 120 second	Symptomatic*
Coagulation profile before/after mixing study	NA*	NA*		76.2/44.5	No Inhibitors
Pre-transfusion of 4 units FFP	< 10%	23	2	65	Symptomatic*
Immediately Post-transfusion of 4 units FFP	23%	18.1	1.4	48	Asymptomatic
4 days Post-transfusion of 4 units FFP	< 10%	23.2	2	67.8	Asymptomatic

Pre-second transfusion of 6 units FFP	<10%	20.9	1.7	53.3	Symptomatic*
Immediately Post-second transfusion of 6 units FFP	36%	15.5	1.2	38.4	Asymptomatic
Pre-third transfusion of 6 units FFP	<10%	21	1.75	57.8	Symptomatic*
Immediately Post-third transfusion of 6 units FFP	35%	15.6	1.2	39.1	Asymptomatic

* Symptoms include epistaxis, gum bleeding.
*NA Not applicable or not done.

Table 3: Classification of severity of hemophilia compared to factor II deficiency

Severity	Hemophilia A, B, C	Factor II Level
Mild	**> 5%**	**> 10%**
Moderate	**1 - 5%**	**≤ 10%**
severe	**< 1%**	**undetectable**