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Case Report

Severe Factor V Deficiency and Thrombin Generation: Case Report in a Woman with a Complication of Uterine Curettage

Sassi M[1]*, Landolsi H[2], Elfaleh R[2], Jlali A[3], Aberrazak F[4], Grafti F[3], Hassine M[4] and Babba H[1]

[1]Biological Laboratory of Maternity and Neonatal Medicine Center, Fattouma Bourguiba University Hospital, Tunisia

[2]Obstetrics Gynecology Department, Fattouma Bourguiba University Hospital, Tunisia

[3]Anesthesiology Department, Maternity and Neonatal Medicine Center, Fattouma Bourguiba University Hospital, Tunisia

[4]Hematology Laboratory, Fattouma Bourguiba University Hospital, Tunisia

***Corresponding author:** Sassi M, Biological Laboratory of Maternity and Neonatal Medicine Center, Fattouma Bourguiba University Hospital, Tunisia

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Abstract

We report the case of a 29-year-old primiparous woman presented with mild metrorrhagia occurring a week after uterine curettage of pregnancy stopped at the 8th week of gestation. Initial laboratory tests found a prolongation of both prothrombin time and activated Partial Thromboplastin Time (aPTT). Mixing her plasma with an equal volume of normal human plasma completely corrected the patient's prolonged aPTT. Liver enzymes and bilirubin levels were within the normal range. Factor (F) V level was 5%. Thrombin generation test was assessed on platelet poor plasma using the Calibrated Automated Thrombogram assay. The chronometric parameters (the lag time and the ttPeak) were significantly prolonged compared to the control experiment (p <0.01). However, the Peak and the ETP were not affected by such a plasma FV level. Metrorrhagia was managed using fresh frozen plasma. Plasma FV level does not correlate with the bleeding phenotype.

Keywords: Factor V; Uterine curettage; Prothrombin time; Activated partial thromboplastin time; Thrombin generation test; Hemorrhagic phenotype

Abbreviations

aPTT: Activated Partial Thromboplastin Time; ETP: Endogenous Thrombin Potential; F: Factor; PT: Prothrombin Time; TFPI: Tissue Factor Inhibitor Pathway; TGT: Thrombin Generation Test; ttPeak: Time to Peak

Case Presentation

A 29-year-old primiparous Tunisian woman, born of non consanguineous parents, presented with mild metrorrhagia occurring a week after uterine curettage of pregnancy stopped at the 8th week of gestation. Immediately after the menarche at the age of 12 years, she manifested occasional abundant menses. She never showed severe bleeding but she reported a history of easy bruising and mucus membrane bleeding. Manifestations included recurrent epistasis and gum bleeding. Moreover, she experienced abundant bleeding during the wedding night and was transported to the emergency, whereas she didn't remember that a clotting factor deficiency was previously mentioned. Different origins of metrorrhagia were excluded before the exploration of haemostatic problem. Initial laboratory tests were as follows: Prothrombin Time (PT) was 22 s (normal, 11-13s), activated Partial Thromboplastin Time (aPTT) was 70s/30s (normal, ≤1.2), thrombin time was 18s/18s (normal, 14-20s), fibrinogen was 3g/l (normal, 2-4 g/l) and platelet count was 285000/mm^3 (normal, 150 000-400 000/mm^3). The Prolongation of PT and aPTT was checked on a second sample. A correction test was planned. Mixing her plasma with an equal volume of normal human plasma completely corrected the patient's prolonged aPTT of 70s to 32.8s and 35.6s before and after 2 hours of incubation at 37°C respectively, indicating the presence of a coagulation factor deficiency and excluding the presence of an inhibitor of the of the common pathway of coagulation. Liver enzymes and bilirubin levels were within the normal range. Clotting factor (F) levels were as follows: FII: 92% (normal, 60-150%), FX: 104% (normal, 60-150%) and FV was 5% (normal, 60-150%). FV measured after 1:1 mixing with normal plasma reached the level of 66%, an increase affirming the FV deficiency. FVIII level was 120% (normal, 50-150%). It was added to eliminate the hypothesis of a combined FV/FVIII deficiency. Thrombin Generation Test (TGT), which is a promising tool to look for hemorrhagic phenotype, was assessed on platelet poor plasma using the Calibrated Automated Thrombogram assay (Thombinoscope b.v, Maastricht, The Netherlands). All measured parameters were analyzed: the lag time, the time to Peak (ttPeak), the Peak and the Endogenous Thrombin Potential (ETP). The values of chronometric parameters were significantly different from those of the control (p <0.01). Indeed, the lag time and the ttPeak were prolonged by 87% and 62% respectively compared to the control experiment. However, the Peak (285 nM *vs.* 317 nM) and the ETP (1403 nMxmn *vs.* 1436 nMwmn) were not affected by such a plasma FV level.

Metrorrhagia was managed by the transfusion of 15 ml/Kg of fresh frozen plasma immediately and of 5 ml/Kg every 12 hours during 5 days. The transfusion was not accompanied by pharmacological treatment such as tranexamic acid. Studies of immediate family members showed that her 86-year-old father and her four brothers had no bleeding history. However, her mother had memories of major bleeding during homebirth and one of her two sisters complained of the same bleeding symptoms (abundant menses, epistaxis and gum bleeding). The patient had given informed consent to participate later to molecular analysis and to search the deficiency through members of her family. She expressed a strong desire to have children. Therefore, she was informed that she had to be closely

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monitored during pregnancy and she received full explanation about the possible hemorrhagic complications during delivery and post-partum. Unfortunately, she didn't return to consultation.

Discussion/Conclusion

Clotting FV, also known as labile factor or proaccelerin, plays an essential role in hemostasis [1,2]. It was described for the first time in 1947 thought the case of a Norwegian woman with bleeding symptoms. Her disorder was named par hemophilia [3,4]. FV is distributed between two pools: 80% of FV circulates in plasma, whereas the remaining 20% is stored in the platelet α-granules [5,6]. Plasma FV is synthesized by hepatocytes and is constituted of a single-chain of 330 kDa [1,5,7], highly homologous to FVIII [5]. The origin of platelet FV, which is physically and functionally distinct from plasma FV [1], is less obvious. Whereas, evidences indicated that platelets and megakaryocytes can both internalize and synthesize FV. FV is a pivotal non-enzymatic cofactor of the prothrombinase complex [1,4,5]. Upon activation, FVa acts as the receptor for FXa and optimizes its ability to cleave prothrombin and to generate thrombin [7]. Interestingly, platelet FVa can initiate prothrombinase activity before plasma FV is activated and sustain this activity long after plasma FVa has been inactivated because of its storage in a partially activated form, its localized release at the site of injury, and its resistance to activated protein C-mediated inactivation. Several data suggest that FV stored and released from platelets is of utmost importance in maintaining normal hemostasis [5].

FV deficiency is a rare autosomal bleeding disorder that reportedly affects 1 per million individuals in the general population [1,7,8]. Although heterozygous individuals for FV deficiency are usually asymptomatic, the homozygous or compound heterozygous for mutations located in the FV gene (F5) show a moderate to severe bleeding disorder depending on the residual FV level [3,5,8]. The most common symptoms are bleeding from mucous membranes (e.g. epistasis, menorrhagia in females) and post-traumatic bleeding following surgery or delivery [1,7]. Particularly, pregnancy and the post-partum are hemostatically challenging to severe FV deficient women [6], but the bleeding manifestation varies dramatically and is poorly correlated with plasma FV level [4,9]. Then, FV deficiency is a serious problem in obstetrics, because both pregnancy and delivery carry a high bleeding risk. Adequate substitution therapy with fresh frozen plasma should be given prior and post delivery to ensure adequate haemostasis [6]. The correlation between FV level and bleeding phenotype is lost in the low FV range (<5%), where patients with equal FV levels may show very different clinical phenotypes [5]. The variable phenotype associated with low or undetectable FV levels strongly suggests the existence of additional factors modulating clinical bleeding in FV-deficiency [9]. Recently, platelet FV and Plasma Tissue Factor Pathway Inhibitor (TFPI) have been identified as phenotype modulators of the bleeding predisposition [2,5,9]. However, the mechanism underlying the preferential localization of FV in platelets rather than in plasma from patients with severe FV deficiency remains unclear [9]. Platelet FV is not routinely determined in FV deficient patients and most studies report only plasma FV levels [9,10]. Moreover, TFPI inhibits both common pathway (FXa) and tissue factor-initiated pathway (TF-FVIIa) [11]. Plasma TFPI level is markedly reduced in FV deficiency. Given that low plasma TFPI levels result in less down-regulation of the TF/FVIIa complex, more FX is likely to be activated in FV-deficient plasma [5]. The TGT measures the overall thrombin activity. It is a promising tool more useful than conventional coagulation tests to look for hemorrhagic phenotype [9]. We have found that the level of 5% of plasma FV is sufficient to ensure thrombin generation that maintains normal coagulation. Using TGT, it was demonstrated that patients with undetectable plasma FV may contain enough functional FV in their platelets to guarantee thrombin generation and protect them against major bleeding [9].

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