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Heterozygous congenital Factor VII deficiency with the 9729del4 mutation, associated with severe spontaneous intracranial bleeding in an adolescent male

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Abstract

Background—In congenital Factor (F) VII deficiency bleeding phenotype and intrinsic FVII activity levels don't always correlate. Patients with FVII activity levels <30% appear to have a higher bleeding propensity, but bleeding can also occur at higher FVII activity levels. Reasons for bleeding at higher FVII activity levels are unknown, and it remains challenging to manage such patients clinically.

Case—A 19 year old male with spontaneous intracranial hemorrhage and FVII activity levels of 44%, requiring emergent surgical intervention and a strategy for FVII replacement. Genotyping showed the rare heterozygous FVII 9729del4 mutation. Bleed evacuation was complicated by epidural abscess requiring craniectomy, bone graft procedures, and prolonged administration of

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Disclosures / Conflict of interest

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Web Resources

The database of the International Society of Thrombosis and Hemostasis was accessed in October 2014, at: https://c.ymcdn.com/sites/www.isth.org/resource/resmgr/publications/fvii_mutations-2011.pdf

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recombinant human (rh) activated FVII (FVIIa). The patient recovered without neurological deficits, and remains on prophylactic low dose treatment with rhFVIIa in relation to risky athletic activities.

Conclusion—For clinicians, it is important to recognize that effects of rhFVIIa within these pathways are independent of its contribution to blood clot formation and cannot be assessed by clotting assays. Reduced FVII levels should therefore not be dismissed, as even a mild reduction may result in spontaneous bleeding. Treatment of mild FVII deficiency requires a careful case-by-case approach, based on the clinical scenario.

Keywords

Factor VII deficiency; spontaneous intracranial hemorrhage; recombinant Factor VII; EPCR

Introduction

Congenital Factor VII (FVII) deficiency is a rare bleeding disorder with a prevalence of 1:500,000 [1]. The clinical presentation is heterogeneous with bleeding complications reported from mild to life-threatening. Bleeding events include intra-cranial hemorrhage, gastro-intestinal bleeding, hemarthrosis, gum bleeding, menorrhagia, among others. While bleeding is more prevalent with low FVII activity levels, there seems no direct correlation between severity of FVII deficiency and bleeding phenotype. Of note severe FVII deficiency can remain relatively asymptomatic, while milder forms can present with life threatening bleeding [1–4].

The etiology for the heterogeneity of bleeding presentations remains elusive, but poses a clinical challenge for acute and prophylactic treatment decisions, especially when FVII activity levels are only mildly or moderately decreased in symptomatic patients.

Here we present a case of spontaneous intracranial hemorrhage in an adolescent male without significant past medical history, subsequently diagnosed with heterozygous FVII deficiency and mildly low FVII activity. This case illustrates that FVII activity levels in FVII deficiency may be deceptive and can underestimate true risk of bleeding.

Case presentation

Clinical presentation

This was a 19 year old male, previously healthy, without reported bleeding history and without bleeding with tonsillectomy and nasal polypectomy in childhood. He presented to the emergency department after feeling a popping sensation associated with a brief loss of consciousness while kneeling. On arrival he was noted to be somnolent without focal neurological deficits. The patient was not on any medication. A toxicology and alcohol screen were negative. Urinalysis, basic chemistry, and complete blood count were within reference ranges. The prothrombin clotting time (PT) was elevated (13.8 s). The activated partial thromboplastin time (aPTT) was within reference range (29.8 s). No other laboratory testing was performed at that time.

Computerized tomography (CT) scan of his head demonstrated an 11 mm subdural hematoma with 5 mm rightward midline shift (Figure 1a). He was discharged in stable condition 24 hours later, but readmitted one week later with increasing lethargy and headaches. CT scan and magnetic resonance imaging (MRI) including angiography revealed the hematoma was stable in size, but the midline shift had increased to 7 mm. The imaging studies ruled out abnormalities that could predispose to bleeding such as tumor, sinus thrombosis, arteriovascular malformation, or aneurysm.

Laboratory results

Laboratory tests pinpointed a mild FVII deficiency in this patient (Table 1). PT was repeatedly prolonged, ranging between 12.6 s and 15.8 s. A 1:1 mixing study (50% patient plasma and 50% normal plasma) corrected the clotting time to within reference range, suggesting a deficiency in the extrinsic pathway. FVII activity levels were repeatedly low at 44%, while the aPTT and activities of clotting factors in the intrinsic and common pathway (II, V, VIII, IX, X, XI) were within reference range (Table 1). These results ruled out subtle deficiencies in the intrinsic or common pathway that would not be detected by the aPTT, but could potentially contribute to bleeding. Elevated fibrinogen levels and a normal reptilase time ruled out hypo- or dysfibrinogenemia. A clot lysis screen and repeated thrombelastographs did not demonstrate accelerated fibrinolysis, making it improbable that severe congenital or acquired abnormalities of the fibrinolytic pathway were contributory.

Vital parameters at presentation

Multiple blood pressure measurements showed a normotensive profile (systolic and diastolic blood pressure < 140 and 90 mmHg), pulse rate ranged from 50 to 70 per minute, respiratory rate ranged from 12 to 18 per minute, and oxygen saturation was 100%.

Personal and Family History

This patient is of Hispanic ethnicity. He has a brother who reported issues with recurrent epistaxis but never requiring emergent care. His parents had no history of bleeding problems. The patient was on no prescription drugs or over the counter medications.

Treatment

The patient was admitted to the Neuro-intensive care unit. Neurosurgery recommended evacuation of the hematoma based on deteriorating symptoms. The patient was started on recombinant human activated FVII (rhFVIIa) (NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) at 19 µg/kg (1 mg total dose) immediately prior to surgery, which was continued every 4 hours through post-operative day 1. He underwent successful evacuation without bleeding complications (Figure 1b). In keeping with the imaging studies, no anatomical abnormalities to explain the spontaneous hematoma were noted by his surgeons. Due to absence of bleeding complications, treatment intervals were increased to every 6 hours through post-operative day 3, and every 8 hours through postoperative day 5. The patient was discharged to home on post-operative day 6 with continued replacement of rhFVIIa at 19 µg/kg every 8 hours through a peripherally inserted central line. Since the estimated risk of recurrence in the first 2–3 months post evacuation by the surgical team was high (~30%),

replacement with rhFVIIa every 8 hours was planned throughout this 3 month period. Unfortunately, the post-surgical course was complicated by an epidural abscess and wound dehiscence requiring craniectomy, empyema wash-out, bone and skin flap procedures as well as a prolonged course of intravenous antibiotics. This required several surgical interventions with periodic intensification of the rhFVIIa substitution to every 4–6h for several days (2–4 days). Due to the protracted course, replacement with rhFVIIa every 8h was continued for approximately 6 months. Assessment of hemostasis was performed clinically since there is no known correlation of laboratory parameters such as PT, FVII activity or thrombelastography with bleeding risk. The patient recovered well without neurological deficits, and was subsequently placed on prophylactic treatment with low dose rhFVIIa at 15 – 20 µg/kg (1 mg per dose) 3 times weekly in relation to high risk sports that the patient was unwilling to forego. There has been no bleeding recurrence two years later at the time of this report. While prophylaxis is usually only recommended for patients with severe FVII deficiency, we weighed the risks and benefits of such practice for this particular patient given his phenotypic presentation with severe intracranial bleeding, his young age, and risky athletic preferences. In comparison to bleeding, we deemed the risk for thrombosis low, based on calculations of estimated molarities of circulating FVII/FVIIa. In plasma, FVII/FVIIa circulates at 10 nM, and the infusion of 1 mg rhFVIIa increases molarity temporarily by approximately 10 nM. This is distinct from replacement therapy in patients with hemophilia and inhibitors, where a dose of 90 µg/kg is administered to achieve plasma FVIIa levels of 40–50 nM.

FVII sequencing

A FVII mutation analysis was performed at the Clinical and Molecular Hemostasis Genotyping Laboratory at Queens University, Ontario, Canada. Polymerase chain reaction primers as described in Wulff *et al.* [5]. Sequencing revealed a heterozygous splice site mutation deletion of GGGT at the exon/intron boundary of exon 7 (9729del4). This mutation results in an insertion of 11 amino acids at position Leu208, and is associated with low levels of protein expression [6].

Informed consent procedures

Data procurement process and patient confidentiality safeguards were approved by the Institutional Review Board. The patient provided written consent.

Discussion

This rare case of a heterozygous 9729del4 FVII mutation highlights the complexity of the relationship between FVII deficiency and clinical phenotype. The diagnosis of mild FVII deficiency in this case was made very late in life, at age 19, after a spontaneous intracranial bleed. Further testing made contributions of other bleeding disorders of the intrinsic and fibrinolytic pathways unlikely. Imaging studies as well as neurosurgical evaluation ruled out any intracranial abnormalities that could predispose to intracranial hemorrhage (ICH).

Diagnosis of FVII deficiency is usually made earlier in life [7], and central nervous system bleeds specifically are observed at an early age in patients with severe deficiency [7, 8],

making this case exceptional. However, a low correlation between FVII activity levels and bleeding diathesis has been previously observed by others [2–4, 9], and is exemplified by our case. Early in life no bleeding problems were reported associated with tonsillectomy and nasal polypectomy, which is puzzling, and is not consistent with the bleeding later in life with the ICH reported here. However, it was this discrepancy, which prompted us to perform the FVII mutation analysis, and report this case. We intended to raise awareness that mild FVII deficiency can be associated with late onset severe bleeding, posing clinical challenges for acute treatment and prophylactic prevention of more life-threatening intracranial bleeding.

Treatment

Management of bleeding episodes in patients with FVII deficiency comprises FVII containing products, and in the United States is typically done with rhFVIIa, approved for this indication. Dosing schedules usually start at 13–30 µg/kg, and entail frequent boluses every 2–6 hours due to short half-life of rhFVIIa (3–6 hours). Despite the short half-life, there is some evidence to suggest that prophylaxis can be useful in preventing bleeding episodes in patients with FVII deficiency. A recent analysis of the international Seven Treatment Evaluation Registry examined 34 patients with severe FVII deficiency defined as levels < 5%. Among 21 patients who received prophylactic doses of rhFVIIa at 90 µg/kg 3 times per week, 14 had an excellent bleeding outcome, defined as no bleeding episodes while on prophylaxis, while 5 had a partly effective outcome, defined as a greater than 50% reduction in bleeding episodes. No thrombosis or inhibitors developed in any of the patients [10].

Since there was no alternative explanation for the ICH in our patient, we deemed the bleeding episode as spontaneous and associated it with heterozygous congenital FVII deficiency. We decided to continue the patient on prophylactic treatment with rhFVIIa, albeit at a low dose of 15 – 20 µg/kg (1 mg per dose) three times weekly to mitigate thrombotic risk given only mildly decreased FVII activity levels and no other bleeding symptoms. This case emphasizes that there is no relationship between severity of congenital FVII deficiency and bleeding phenotype, and that mild congenital FVII deficiencies can result in severe bleeding. Reasons may be inherent to the fact that FVII is not just important for rapid thrombin and clot formation, but also for vascular barrier function, which cannot be captured with clotting assays. These are critical considerations for clinical decision making when encountering patients with congenital FVII deficiency.

Mutation analysis

A literature search in the database of the International Society of Thrombosis and Hemostasis (ISTH) for FVII mutations causing rare bleeding disorders revealed that this mutation (FVII 9729del4) has previously been reported in the literature. The first report was from a study in 1998 of three Italian patients. In that study, one patient had this deletion, which was discovered after referral for a prolonged PT in pre-surgery screening. The patient was heterozygous for the mutation, with a FVII activity level of 61% (58% antigen), and the mutation was found also in the patient's granddaughter with 47% FVII activity (42% antigen) [6]. In a study by Millar *et al.* [2], two probands of Spanish origin had the identical

heterozygous mutation. The probands presented with a moderate bleeding phenotype and had FVII activity levels of 50% and 55%, both with 50% antigen. In a study of a German FVII database the mutation was reported in a proband who presented with a FVII activity level of 27% (antigen level not reported) [5].

The mutation involves a deletion of one copy of a 4 base pair (bp) direct repeat within the first of several 37 bp repeats that lie 3' to exon 7. This deletion affects mRNA splicing and results in an in-frame insertion of 11 amino acids between Leu208 and Gly209. Expression of cDNA of this FVII mutant in baby hamster kidney (BHK) cells revealed that the mutant protein was produced by the cells, but expression into the culture medium was severely reduced [6]. This suggests that the mutant protein may be produced by patients carrying the mutation, but very little of it is transported out of the cells into the blood. If both alleles of the gene are expressed, this could explain the approximate 50% FVII antigen found in heterozygous patients with the residual ~50% of FVII antigen coming from the wild-type gene. However, to our knowledge it has not yet been determined if the residual FVII antigen in heterozygotes consists of WT protein, mutant, or both.

Genotype / phenotype correlation in FVII deficiency

A FVII gene mutation analysis of 717 patients participating in the Greifswald Registry of FVII Deficiency detected 131 different mutations in 73 homozygous, 145 compound heterozygous, and 499 heterozygous patients [4]. Homozygotes and compound heterozygotes were symptomatic with bleeds, 71% and 50% respectively. Only 19% of heterozygotes presented with bleeds. Among heterozygotes, 28 different mutations were found, no significant correlation with phenotype for any specific mutation was found, and no severe bleeding was reported for any of these patients. It can be hypothesized that environmental factors may influence reported FVII levels. A well-known example of inter-lab variability is the type of tissue factor used to measure activity levels of FVII [11].

In an analysis of 489 patients registered in the European Network of Rare Bleeding Disorders, which included 224 patients with FVII deficiency a strong association was found between coagulation factor activity level and clinical bleeding severity for those patients with deficiencies of fibrinogen, FX, FXIII, and combined FV and FVIII deficiencies [3]. However only weak associations with FV and FVII deficiencies were found, and no association between phenotype and FXI levels, indicating a very heterogeneous association between factor activity levels and bleeding phenotypes among rare bleeding disorders. This may be explained by differences in mutations in the FVII gene, which may express different levels of coagulant activity resulting in varying qualitative defects.

Interactions of FVII with EPCR

FVII and FVIIa have been shown to bind to endothelial protein C receptor (EPCR) [12–14]. This receptor is well known for its ability to bind protein C (PC) and contribute to the activation of PC in the EPCR-PC-thrombomodulin-thrombin complex, to form activated PC (APC). APC exercises anti-coagulant effects by proteolytically inactivating activated factors V and VIII. Furthermore, APC can bind to EPCR to exert cytoprotective, anti-apoptotic, and

barrier-protective effects, mediated by APC cleavage of protease activated receptors (PAR) [15–18].

The Gla-domain of FVII and FVIIa can bind to EPCR with similar affinity compared to the APC-EPCR interaction [12]. EPCR is critical to maintain vascular barrier function [19] and FVIIa can mediate barrier protective effects via the EPCR-PAR1 signaling pathway [20, 21]. A decrease in FVIIa activity, as seen in the 9729del4 mutation, could therefore potentially diminish protective signaling via this pathway resulting in vascular instability.

In addition, translocation of FVIIa from the circulation to the extravascular space requires EPCR [22, 23]. Extravascular localization of FVIIa seemed defined by the presence of tissue factor expressing cells, and perivascular tissue factor is occupied with endogenous FVII/FVIIa [24, 25]. Although FVII and FVIIa are cleared from the circulation relatively fast (3–6 hours), FVIIa in the perivascular space is remarkably stable with functional activity detectable for at least 7 days [23]. The current paradigm assumes that FVII/FVIIa in the perivascular space provides a hemostatic reserve that helps ameliorate the risk of bleeding [23, 26]. Hence, there is some thought that the prophylactic effects of FVIIa in hemophilia patients may be attributed to these extravascular reserves of FVIIa. However, definite evidence is lacking. Because the rate of FVIIa translocation is dependent on the expression level of EPCR, it is likely also dependent on the concentration of FVII. These FVII perivascular hemostatic reserves, therefore, might become exhausted when FVII levels are persistently low, such as due to the 9729del4 mutation. Therapeutic or prophylactic administration of recombinant FVIIa restores the perivascular reserves of FVIIa, which in mice are saturated 8 hours post injection [23].

Structure/function

FVII/FVIIa and APC interact with EPCR via their Gla-domain, with Leu8 being the most important residue [14]. It is therefore unlikely that the 11 amino acid insertion (GTTLPCTAVL) between Leu 208 and Gly209 in the protease domain of the 9729del4 variant will disrupt interaction with EPCR. Looking at FVII in standard view (with Gladomain down, and active site facing forward) residues Leu208 and Gly209 are located on top of the protease domain, remote from the EPCR binding site. Pinotti *et al.* [6] suggested a theoretical model where the 11 amino acid insertion produced a new loop on the surface of the FVII proteolytic domain, and caused a structural change in the protein by setting Leu208 and Gly209 10Å apart. Such a structural change could affect the activity of the molecule and potentially disrupt interactions with natural substrates, inhibitors, and other binding partners.

In summation, decreased activity of FVII due to the 9729del4 genotype leads to decreased coagulation activity of FVII and may potentially result in diminished vascular protective cell signaling. However, it is possible that an expression defect prevents 9729del4 mutant FVII from reaching the circulation causing depletion of extravascular FVII reserves. More studies are required to determine the potential contributions to a bleeding phenotype for each of these possibilities.

Conclusion

This case of spontaneous intracranial hemorrhage in a patient with mildly reduced FVII level due to a heterozygous FVII mutation, illustrates that FVII activity levels do not correlate well with bleeding phenotype. For clinicians, it is important to recognize that FVII may have protective effects that are independent of its contribution to blood clot formation and cannot be assessed by clotting assays. Reduced FVII levels should therefore not be dismissed, as even a 50–60% reduction can result in spontaneous bleeding. The treatment algorithm using frequent recombinant human FVIIa replacement therapy during the bleeding episode and surgical interventions, as well as the low dose prophylactic replacement with risky athletic activities, were derived from a careful risk benefit analysis that included input from the neurosurgical and neurocritical care teams. This approach proved to be safe and protective for this particular patient. However, treatment algorithms for mild FVII deficiency cannot be easily generalized and require a careful case-by-case approach, based on the clinical scenario.

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Figure 1A

Figure 1B

Figure 1.

A) CT head on presentation. B) CT head post evacuation. CT, computerized tomography.

Table 1

Laboratory results. WBC, white blood cell count; PT, prothrombin time; aPTT, activated partial thromboplastin time. Reference ranges: FII 75–125%, FV 55–135%, FVIII 55–140%, FIX 65–135%, FX 60–135%, FXI 75–165%.

Lab test	Value	Reference value
Clot lysis screen	Normal	Clot stable in 5M urea at 24 hours
Factor VII activity level	44%	60% – 120%
Factors II, V, VIII, IX, X, XI	Normal	Within reference range
Fibrinogen (mg/dL)	641	200 – 450
Hemoglobin (g/dL)	12.9	13.7 – 17.5
Platelets ($\times 10^3$ cells/ μ L)	299	140 – 370
Prothrombin Time (s)	15.8	9.7 – 12.5
PT 1:1 mixing study (s)	11.9	9.7 – 12.5
aPTT (s)	30.5	25 – 34
Reptilase time (s)	13.8	Control $\pm$ 4
WBC ($\times 10^3$ cells/ μ L)	12.5	4.0 – 10.0