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REVIEW

Phenotypical variability in congenital FVII deficiency follows the ISTH-SSC severity classification guidelines: a review with illustrative examples from the clinic

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Background: One of the most common rare inherited bleeding disorders, congenital factor VII (FVII) deficiency typically has a milder bleeding phenotype than other rare bleeding disorders. Categorizing severity in terms of factor activity associated with hemophilia (severe <1%, moderate 1%–5%, mild 6%–40%) has led to the observation that bleeding phenotype does not follow closely with FVII activity. Over the past decade, large-scale global registries have investigated bleeding phenotype more thoroughly. The International Society on Thrombosis and Haemostasis has reclassified FVII deficiency as follows: severe, FVII <10%, risk of spontaneous major bleeding; moderate, FVII 10%–20%, risk of mild spontaneous or triggered bleeding; mild, FVII 20%–50%, mostly asymptomatic disease.

Case reports: Eleven illustrative cases of congenital FVII deficiency adapted from clinical practice are described to demonstrate the variability in presentation and in relation to FVII activity levels. Severe FVII deficiency usually presents at a young age and carries the risk of intracranial hemorrhage, hemarthrosis, and other major bleeds. Moderate FVII deficiency tends to present later, often in adolescence and particularly in girls as they reach menarche. Milder disease may not be apparent until found incidentally on preoperative testing, during pregnancy/childbirth, or following unexplained bleeding when faced with hemostatic challenges.

Conclusion: It is important for health care professionals to be aware of the new definitions of severity and typical presentations of congenital FVII deficiency. Failure to appreciate the risks of major bleeding, including intracerebral hemorrhage in those with FVII activity <10%, may put particularly young children at risk.

Keywords: blood coagulation disorders/classification, blood coagulation factors/physiology, humans' rare diseases/classification, Severity of Illness Index

Plain language summary

Congenital FVII deficiency is a rare bleeding disorder caused by faults in genes coding for clotting factor VII, meaning that levels are not high enough to allow normal blood clotting. Congenital FVII deficiency is associated with lower amounts of bleeding than other types of rare bleeding disorder. Over the past decade, large studies on congenital FVII deficiency have helped classify this disorder as severe, moderate, or mild, based on the amount of clotting factor VII produced and the risk of bleeding.

To help show the variation between bleeding symptoms and the amount of clotting factor VII produced, illustrative cases were adapted from eleven patient profiles seen in the author's clinics. Our results highlight that severe FVII deficiency is usually discovered at a young age and carries a risk of major bleeds, including bleeding within the skull and joints. Moderate

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FVII deficiency is usually found in adolescents and in girls starting their menstrual cycle (periods). Mild forms of the disorder are more difficult to find and may only be discovered by chance during pregnancy/childbirth or during major bleeding caused by an injury or surgery. It is important that health care professionals understand the classifications of congenital FVII deficiency and the associated risks of major bleeds, particularly in patients with the severe form of this disorder.

Introduction

Congenital factor VII (FVII) deficiency is an autosomal recessive inherited bleeding disorder resulting from defects in the genes coding for clotting FVII. Historically referred to as hypoproconvertinemia, it is recognized as the most frequently presenting rare bleeding disorder (RBD).[1] It is estimated to affect 1 in 500,000 people,[2] and is most prevalent in areas where consanguinity exists.[3] Males and females are affected equally; however, females are more likely to have symptomatic disease as a result of gynecological or mucocutaneous bleeding.[4,5]

Reviews in the literature suggest that bleeding symptoms in those with congenital FVII deficiency cannot easily be predicted by severity classification.[6] This observation is based upon the application of the hemophilia severity categorization (severe: <1%; moderate: 1%–5%; mild: 6%–40%; normal: 50%–150%) to FVII activity; this categorization method is now considered to be outdated. Based upon a physician-reported, 4-level scale, results from the European Network of Rare Bleeding Disorders (EN-RBD) registry demonstrated a varied association between coagulation factor activity level and clinical bleeding in RBDs.[6] Different categories of bleeding phenotype were associated with slightly overlapping ranges of factor activities for each disorder. Of 592 patients in the EN-RBD registry, 234 (40%) had congenital FVII deficiency. Linear regression analysis of FVII activity showed that factor activity for asymptomatic patients was 24.9%: for grade I bleeding (after trauma): 19.1%; for grade II (spontaneous minor bleeding): 13.4%; for grade III (spontaneous major bleeding): 7.7%.

Based on these EN-RBD data, the International Society on Thrombosis and Haemostasis Scientific Standardization Committee (ISTH-SSC) recommended a new classification system for RBDs, including congenital FVII deficiency.[6] In contrast to the classification of congenital hemophilia based upon factor VIII or factor IX activity, for congenital FVII deficiency, severe disease is defined as FVII activity <10% (with greatest risk for spontaneous major bleeding), moderate deficiency 10%–20% (patients are at risk for mild spontaneous or triggered bleeding), and mild deficiency 20%–50% (usually an asymptomatic course).

This article details the 2012 ISTH-SSC classification guidelines on congenital FVII deficiency. It presents brief, illustrative case vignettes adapted from patient profiles seen in the authors' clinics that highlight not only the variability seen in patients, but also how the disease classification process has been improved by the introduction of the guidelines.

Case descriptions

Severe deficiency: three examples of early presentation

The first patient, a male infant diagnosed with severe FVII deficiency as a newborn, presented with an intracerebral hemorrhage (ICH), aqueductal stenosis, and hydrocephalus. Preoperative coagulation testing performed prior to placement of a ventriculoperitoneal shunt showed an elevated prothrombin time (PT) at more than twice normal; subsequent testing revealed FVII activity of 2%. His first year was complicated by recurrent ICH, meningitis, seizures, and repeated neurosurgical procedures requiring FVII replacement. Now, at 8 years of age, his FVII activity is 4%–8% (severe deficiency), yet he has minimal symptoms with only occasional bruising. Family history and evaluation revealed his father is a carrier and his mother has normal FVII levels. His 9-year-old sister has mild FVII deficiency and has been asymptomatic, although has not yet reached menarche.

A 9-month-old female was transferred to a tertiary hospital after 4 days of bloody diarrhea up to three times an hour. Two days into symptoms, she was evaluated in the emergency room and found to be slightly anemic (hemoglobin: 10.3) with unmeasurable PT (eg, >100) and normal activated partial thromboplastin time (aPTT). An abdominal ultrasound was unremarkable. She received 3 days of vitamin K and was transferred to a hemophilia treatment center (HTC), where further testing revealed an FVII activity <1%. The presumed diagnosis was gastroenteritis complicated by FVII deficiency. Family history revealed a sister with severe FVII deficiency. Her mother had normal FVII activity levels. Subsequent to hospital discharge, the patient had multiple episodes of oral bleeding over 2–3 months, each successfully treated with replacement therapy. At 13 months of age, she presented with a 3-day history of left ankle swelling and pain and refused to bear weight on her foot. An X-ray showed a large tibiotalar joint effusion without fracture, and she was treated for a left ankle bleed with FVII replacement therapy.

In the third severe deficiency case, a 4-year-old female presented with ongoing pain and swelling in the left ankle. About 6 months earlier, she had fallen and fractured her left distal fibula (Salter–Harris I fracture), which required cast placement. Her mother reported that following removal of the cast, she continued to have pain in the left ankle along with limping and swelling, which prompted follow-up with orthopedics. Both of her ankles showed bogginess over the lateral malleolus, despite no history of right ankle trauma. Her bleeding history was notable for a previous left arm injury with soft-tissue bleeding, mucosal bleeding with teeth eruption, and easy bruising. She has a 2-year-old sister with severe FVII deficiency with undetectable FVII activity. Her mother's FVII activity was within the lower limit of normal. In light of her sister's diagnosis and suspected ankle bleeding, the patient underwent laboratory evaluation, revealing FVII activity <1%. Radiographic studies of the ankles showed changes suggestive of arthritis of the right ankle.

Moderate deficiency in an adolescent

A 13-year-old female first presented at 11 years of age with excessive bruising on her legs (disproportionate to injury) and spontaneous bruising in unexposed areas, for example, her back, upper arms, and thighs. She reported a history of prolonged oozing from minor cuts, heavy menstrual bleeding (HMB), and prolonged bleeding after tonsillectomy/adenoidectomy at 4 years of age. Workup at the pediatrician's office revealed prolonged PT (19.4 seconds) and normal aPTT, which vitamin K did not correct. A referral was made to an HTC, where she was found to have moderate FVII deficiency (FVII: 14%). Family history was notable for her mother displaying easy bruising, epistaxis, and HMB, as well as a FVII level at the lower end of normal. The patient received replacement factor therapy before wisdom tooth extraction at 13 years of age. Her HMB has been effectively treated with oral agents.

Five mild deficiency cases: early childhood to adulthood

A 41-year-old female was evaluated for liver lesions; she had an elevated PT and international normalized ratio (INR). Upon referral to an HTC for evaluation of an elevated INR, mild FVII deficiency was confirmed (FVII activity 26%). Her medical history showed she had easy bruising and epistaxis dating back to childhood. Her first hemostatic challenge was wisdom teeth extraction (×4) in her 20s, followed by excessive bleeding requiring multiple gauze pad exchanges. HMB commenced with menarche at 12 years and she experienced postpartum hemorrhage after delivery of her second child with a significant drop in hemoglobin. She currently has epistaxis once weekly in the winter lasting 30 minutes and resolving with pressure, gum bleeding when brushing her teeth with a hard toothbrush, and hemorrhoidal bleeding. Family history revealed that her son has epistaxis during winter only and her daughter has HMB; neither has been tested for FVII deficiency.

The second case, a 21-month-old female, presented with recurrent bouts of hematemesis secondary to respiratory issues leading to coughing episodes. Her medical history included tetralogy of Fallot (surgically repaired), gastroesophageal reflux, chronic stridor, and subglottic stenosis. Workup revealed prolonged PT and mild FVII deficiency (FVII: 27%–30%). She experienced heart surgery prior to diagnosis and multiple bronchoscopies following diagnosis without bleeding complications, and has not required FVII replacement therapy in the peri- or postoperative period. Her mother had no bleeding history and had normal FVII activity levels.

A 14-year-old male first presented with increased bruising at 5 years of age without other bleeding symptoms. His medical history revealed myringotomy with tubes at 2 years without postoperative bleeding. He was found to have a slightly prolonged PT; other laboratory values were normal (aPTT, fibrinogen, von Willebrand factor, platelet function). His FVII activity was consistent with mild deficiency (FVII: 28%–36%). Following diagnosis, he was empirically infused with replacement factor therapy once in an emergency situation after having concussion from falling off a golf cart and was later found to have a negative head computed tomography (CT). His parents had mild FVII deficiency. His half-sister had HMB and was found to have mild FVII deficiency.

At 12 years of age, a female was referred for evaluation of HMB, with no other bleeding symptoms. She was found to have mild FVII deficiency (FVII: 47%) along with concurrent low FV activity (56%; reference range: 70%–120%). Family history revealed that her mother had HMB and bleeding after wisdom tooth extraction, but testing revealed normal FVII levels in both parents.

An asymptomatic 11-year-old male was found to have prolonged PT during a routine clearance examination for a sporting activity. He had no history of bleeding symptoms. He had an uneventful circumcision at birth and a concussion from playing American football at 10 years of age (negative CT scan). Further testing showed that he had mild FVII deficiency (FVII: 29%–34%). Family history revealed his mother had HMB and microscopic hematuria, but had

normal FVII levels. His two maternal aunts and maternal grandmother also had a history of HMB and microscopic hematuria (FVII activity unknown). His father's FVII activity level was mildly low.

Moderate deficiency with prothrombotic FVII mutation

A 17-year-old male was diagnosed with FVII deficiency following an uncomplicated appendectomy at 4 years of age, when he was found to have elevated PT. Further evaluation revealed moderate FVII deficiency (FVII: 17%). He had no history of bleeding symptoms. The patient was also noted to have a heterozygous mutation in the PT gene (G20210A). This testing was prompted by a positive family history and is associated with a hypercoagulable state.

Mild deficiency in an elderly male taking concurrent anticoagulant

A 78-year-old male with a history of squamous cell carcinoma metastatic to the head presented to the emergency room with increased confusion. A head CT was performed and a recurrent mass identified; this prompted neurosurgical consultation for craniotomy. The patient was taking anticoagulation with warfarin for chronic atrial fibrillation. His preoperative course was complicated by the failure of vitamin K to completely reverse prolonged PT/INR. This prompted further evaluation, which revealed mild FVII deficiency (FVII: 30%). His medical history revealed no prior bleeding symptoms, no bleeding on warfarin therapy for the previous 2 years, and no bleeding with a prior craniotomy 8 years ago.

Discussion

Congenital FVII deficiency is characterized by a wide range of clinical presentations with ~30%–40% of affected individuals having asymptomatic disease.[4,5] Life-threatening bleeds (eg, intracranial hemorrhage, gastrointestinal [GI] bleeds) and hemarthrosis are usually seen early in life, <6 months and <5 years of age, respectively.[4] The most frequent presenting symptom is epistaxis.[4,7]

A variety of causative molecular defects have been identified, with missense mutations being the most common.[8] However, unlike hemophilia A and B, mutation type does not provide insight into the expected severity of the bleeding diathesis. In general, patients with missense mutations are more likely to have mild asymptomatic disease, but this is not an absolute.[8] Homozygous and compound heterozygous patients have similar clinical bleed patterns and are more likely to manifest with severe symptoms compared with heterozygous patients.[4,7]

Half of the patients are diagnosed within 6 months of symptom onset;[4] however, those with less severe disease may experience significant gaps between symptom onset and diagnosis.[4,5,9] Abnormal PT in the presence of normal aPTT usually raises the suspicion of FVII deficiency.[10,11] Functional and immunological assays can determine residual protein and antigen levels.[11] As with mutation status, bleed risk cannot be reliably determined by FVII activity.[6,8]

Disease classification systems are commonly based on predictors of disease severity and help to define the clinical course of a disease. For bleeding disorders, classifications are generally made by understanding the relationship between disease severity and residual clotting factor activity level. While it is possible to use factor activity as a diagnostic criterion and predict bleeding severity in congenital hemophilia and some RBDs (eg, factor XIII [FXIII] or factor X deficiency), this association is not as strong in congenital FVII deficiency.[6]

Before the EN-RBD's approach of grading bleeding phenotype on a 4-level scale, observations about the lack of correlation of FVII activity with phenotype have been limited by applying a hemophilia-like classification (mild/moderate/severe) to FVII deficiency. Giansily-Blaizot et al evaluated the predictive ability of FVII activity to identify the risk of severe bleeds in 42 FVII-deficient patients with FVII activity <30%. Using receiver operating characteristic curve analysis, the authors concluded a threshold level for FVII activity at 8%, that is, patients with levels >8% had a low risk of severe bleeds (defined by the authors as bleeds requiring blood products or FVII replacement therapy).[12] However, in this and other studies, some patients under the threshold level displayed mild disease or were otherwise asymptomatic.[12] Cases of late-onset ICH with no previous history of bleeding, despite hemostatic challenges and a FVII activity of 44%, highlight the challenge of identifying high-risk individuals through FVII activity alone.[13]

In an attempt to leverage the large body of data from RBD registries, the EN-RBD database was analyzed for an association between residual plasma concentrations and clinical course across rare factor deficiencies. Bleeds were reviewed and graded for severity based on a 4-level scale developed through consensus of clinicians at participating sites. Congenital FVII deficiency was found to be one of the mildest rare factor deficiencies: 54.7% were asymptomatic; 16.7% had provoked bleeding with trauma (grade I); 21.7% had spontaneous mild bleeding (grade II); and only 6.9% had

spontaneous major bleeding (grade III). In contrast, 48.5% of those with FXIII deficiency and 42.3% with fibrinogen deficiency had spontaneous major bleeding (grade III). The linear regression approach established that the minimum FVII activity to keep a patient asymptomatic was 25% and the factor activity associated with spontaneous major bleeding was FVII <8%.[6]

The RBD Working Group, under the umbrella of the Factor VIII and Factor IX ISTH-SSC, then conducted a broader review of RBD registries in the UK, the US, and India, as well as of literature with cases that explored the laboratory–clinical association of RBDs. Without contradiction from the other sources evaluated, the working group used the EN-RBD data to establish a severity classification system for each RBD. They defined three levels of severity based on the coagulant level most likely associated with spontaneous major bleeding (severe), mild spontaneous or triggered bleeding (moderate), and mostly asymptomatic disease course (mild). The heterogeneity in the strength of association between clotting factor activity level and specific activity thresholds linked to clinical phenotype led the working group to propose unique factor concentration–severity definitions for each of the RBDs, with FXIII deficiency being one of the most severe (limited activity assays available for lower levels, severe is defined as undetectable activity, moderate is <30% activity, and mild or asymptomatic is >30% activity). For FVII deficiency, the residual factor level associated with severe disease is <10%, for moderate disease 10%–20%, and for mild disease >20%.[14]

The weak association between genotype, FVII activity, and phenotype has led some investigators to evaluate the ability of presenting bleeding symptoms to predict subsequent risk of bleeds, and thus to provide insight into potential therapeutic interventions. Data were evaluated from multinational registries on 626 individuals with either a spontaneous bleed event at presentation or diagnosis made through family history or preprocedure hemostatic studies; registries included the International Registry on Congenital Factor VII Deficiency and Seven Treatment Evaluation Registry (STER).[15] Bleeding in a critical area or organ was defined as major bleeding (central nervous system, GI, or joints) and mucocutaneous bleeding (excluding GI) as minor bleeding. Individuals were categorized as major bleeders (≥1 major bleed), minor bleeders (no history of major bleeding episode or mucocutaneous bleed event), or asymptomatic. Lifelong bleed risk was 1.79 times greater in individuals experiencing a major bleed with their index event vs those having a minor bleed (95% CI: 1.23–2.6; *P*=0.003). Both major and minor bleeders at presentation had at least one subsequent event (98.7% and 97.1% of patients, respectively). Only 12.1% of nonbleeders at diagnosis had a subsequent event during the observation period (median 9.12 years). Thus, the relative risk of any bleeding event was significantly higher in individuals presenting with major or minor bleeding events vs those who were asymptomatic at diagnosis.

To clarify bleeding risk, clotting activity was investigated in these same groups. A high proportion of major bleeders had FVII activity <3% at presentation and during follow-up (58.4% and 65.6%, respectively); however, some with minor bleeding at presentation and follow-up also had low factor levels (46.6% and 37.2%, respectively), as did a smaller percentage of nonbleeders (8.8% and 8.5%, respectively).

Certain index bleeding events carried a higher risk of a subsequent major bleeding event. Relative risk of a subsequent major bleed was 2.56 (95% CI: 1.19–5.48; *P*=0.016) for index bleeds involving the umbilical cord stump and 3.35 (95% CI: 1.57–7.18; *P*=0.002) for muscle or subcutaneous hematomas.

A further evaluation of the International Registry on Congenital Factor VII Deficiency and STER databases, looking at sex-related differences, demonstrated that mucocutaneous bleeding at index bleed has significant risk for lifelong gynecological bleeding events in women. Women with FVII activity <3% had nearly three times greater risk of lifelong gynecological bleeding compared with those women whose levels were 3%–26% (hazard ratio: 2.8, 95% CI: 1.308–6.002; *P*=0.008).[5]

In 2014, James et al reviewed the potential application of bleeding assessment tools (BATs) for standardizing bleeding histories and distinguishing unaffected from affected individuals with RBDs.[16] In reviewing the development of multiple instruments, the authors cite studies of 594 patients with RBDs, including FVII deficiency, often in the setting of evaluating patients with either symptomatic bleeding or abnormal coagulation studies, although most tools were first developed for more common disorders, for example, von Willebrand disease (VWD). The Pictorial Bleeding Assessment Chart published by Higham et al in 1990 was one of the earliest to evaluate HMB by tracking the number of pads/tampons used per menstrual period and the degree of soiling. Pictorial Bleeding Assessment Chart scores ≥100 correlate with menorrhagia, defined as ≥80 mL menstrual blood loss.[16,17] In 2005, the ISTH-SSC on von Willebrand factor established criteria for the diagnosis of VWD type 1, including a threshold for mucocutaneous bleeds;[18] by 2010, the BATs developed around diagnosis of VWD[19–22] coalesced

into the ISTH-BAT.[16,21] Tosetto et al studied 215 patients with possible bleeding disorders. The diagnostic efficiency of the BAT (sensitivity, specificity, and predictive value) depended on the reason for referral (bleeding symptoms, family history, or abnormal clotting test), implying a different underlying prevalence of a bleeding disorder.[16,23] For example, specificity was highest for a mild bleeding disorder in those with abnormal clotting test results (0.98). Using a BAT to exclude a mild bleeding disorder and avoid further testing requires high sensitivity and negative predictive value; identifying patients with a mild bleeding disorder to initiate treatment requires high specificity and positive predictive value.[16,23]

The simplified, adapted cases of congenital FVII deficiency presented here were drawn from clinical practices of the authors, not from a specific retrospective chart review, to illustrate the variability in presentation and relation to FVII activity levels. Severe FVII deficiency (first three cases) usually presents in young children; it has a risk of ICH and other major bleeds (eg, GI bleeding), as well as hemarthrosis. The two moderate FVII deficiency cases show that it typically presents later, for example, in adolescence and especially in girls reaching menarche. Epistaxis, bruising, HMB, and bleeding complications in pregnancy are often seen. The final cases describe milder disease and how it may not be diagnosed until found incidentally on preoperative testing, during pregnancy/childbirth, or following unexplained bleeding in those circumstances. There are other factors that may impact bleeding phenotype: concomitant thrombophilias that increase the risk of clotting (factor II mutation in penultimate case) and might reduce the likelihood of bleeding; and concurrent anticoagulants (final case) that might increase bleeding risk.

While psychosocial issues and the need for comprehensive care in congenital hemophilia have been extensively studied,[24–30] the need for comprehensive management of patients with congenital FVII deficiency is no less important. Even within the HTC networks, experience with moderate-to-severe FVII deficiency is variable. Collaboration around focused data collection can inform a better understanding of the natural history of congenital FVII deficiency and identify better practices in management (eg, pregnancy, treatment around major/minor procedures) to improve quality of care. Issues around transition periods with impact on school, work, and relationships are seen across all bleeding disorders and warrant involvement of experienced nurses and social workers with patients and their families, as well as schools and employers. Those affected with arthropathy and those engaging in moderate-to-vigorous physical activity could benefit from periodic physical therapy evaluation. In the US, infrastructure for genotyping is needed, as is genetic counseling (even based upon screening families with FVII activity); these may lead to improved care.

Treatment of FVII deficiency has progressed significantly with data from the International Registry on Congenital Factor VII Deficiency[31] and STER[5,32–35] over the past decades. In particular, STER prospectively collected data on management of patients with systematic analysis of treatment-related adverse events,[34] including as part of post-marketing surveillance of recombinant activated FVII (NovoSeven® RT; Novo Nordisk, Bagsværd, Denmark). The STER investigators have published on treatment of 101 bleeds in 75 patients,[33] 41 surgical operations (24 major, 17 minor) in 34 subjects receiving recombinant activated FVII,[32] and 38 courses of prophylaxis in 34 patients receiving any FVII product.[35] Recent reviews have also focused on treatment options for women with FVII deficiency[5] and for patients with FVII deficiency and other RBDs.[36]

Conclusion

Health care professionals should be aware of the new ISTH-SSC severity classification of FVII deficiency and the type of bleeding likely to be seen within each category. Failure to appreciate the risks of spontaneous major bleeding, such as ICH and other life-threatening bleeds, in those with FVII activity <10% (severe deficiency) may put young children at risk. This is especially important given the historical view of FVII deficiency as a disorder with a mild bleeding phenotype where symptoms do not typically correlate with FVII activities.

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