

CASE REPORT

Late diagnosed factor VII deficiency – a rare but significant haemorrhagic diathesis

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ABSTRACT

Factor VII (FVII) deficiency is a rare but significant inherited autosomal recessive coagulation disorder, occurring with a frequency of 1 in 300,000-500,000 people. The disorder is characterised by a wide range of bleeding symptoms that do not always correlate with plasma FVII levels, from asymptomatic conditions to severe haemorrhages. We present the case of a 2-year-old boy who was admitted to hospital for prolonged nosebleeds. Laboratory tests showed significant coagulation abnormalities: prolonged prothrombin time and international normalised ratio, directing suspicion to a rare coagulation disorder. Further diagnostics at a specialised centre confirmed congenital factor VII deficiency. The boy was observed to have repeated episodes of nosebleeds, and haematoma formation in the area of the knees, elbows, and fingers, even with minor trauma. Factor VII deficiency is a rare coagulation disorder, so each described case is important to better understand the clinical spectrum and therapeutic options.

KEY WORDS:

factor VII deficiency, FVII laboratory assay, rare bleeding disorders.

INTRODUCTION

Factor VII (FVII) is a vitamin K-dependent glycoprotein that is synthesised in the liver. In its active form (FVIIa), it interacts with tissue factor (TF) to initiate the extrinsic clotting pathway.

The FVIIa/TF complex becomes an activator of factor X (FX), activating it in the presence of calcium ions. Activated factor X (FXa) is released from platelets and binds to tissue phospholipids. FXa then combines with factor V, forming a complex that activates prothrombin, which subsequently converts to thrombin in the presence of calcium ions, and the clotting process continues [1].

FVII deficiency is a rare but significant disorder of the coagulation system, occurring with a frequency of

1 in 300,000 to 500,000 people. It is inherited in an autosomal recessive manner and can manifest in all age groups, with the median being 8 years [2, 3].

There are 2 types of this abnormality. The first results from insufficient synthesis of the molecule along with increased consumption, while the second arises from the synthesis of an abnormal molecule [1, 2].

The clinical manifestations of FVII deficiency are extremely diverse, ranging from an asymptomatic course and incidental diagnosis to severe bleeding, including into the central nervous system or gastrointestinal tract. The most common findings are nosebleeds, gum bleeding, a tendency to bruise, recurrent joint bleeding, or heavy menstruation [4, 5]. Laboratory tests show a prolonged prothrombin time (PT) and reduced FVII levels [3].

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FVII deficiency can also be acquired as a complication of serious medical conditions: sepsis or malignancies [4–6].

Acquired causes of FVII deficiency include vitamin K deficiency or absorption, anticoagulant therapy with vitamin K antagonists, and the effects of liver disease. Additionally, severe systemic sepsis and malignancies have been associated with acquired FVII deficiency, which has also been reported in patients undergoing haematopoietic stem cell transplantation. Several pathomechanisms have been postulated to explain the condition: the presence of an inhibitory antibody to FVII, sequestration of FVII by a large pool of tissue factor in the extravascular space, or the elimination of FVII from the circulation by abnormal fixation to tumour cells [7].

CASE REPORT

This case has been presented for educational purposes to enhance vigilance among physicians. We hope that the analysis of this case will contribute to improving diagnostics and treatment, thereby raising the quality of patient care.

A 2-year-old boy was referred to district hospital because of prolonged, unstoppable nose bleeding. Medical history: previously healthy, not under the care of any specialist clinic, and vaccinated according to the vaccination calendar. Family history of coagulation disorders was negative.

During hospitalisation, laboratory tests showed significant abnormalities: PT: 163 seconds, international normalised ratio (INR): 12.84. To extend the diagnosis, the boy was referred to the Department of Paediatric Hematology, Oncology, and Transplantology at the University Children's Hospital in Lublin. Detailed investigations were carried out there to determine the cause of the abnormalities in haemostasis, taking into account the possibility of a rare coagulation disorder. The results are shown in Table 1.

Based on the test results, congenital FVII deficiency was diagnosed. A consultative study was performed at the Regional Blood Donation and Haematology Centre, which confirmed factor VII deficiency (results in Table 2). Subsequent tests showed significantly reduced FVII activity of 7% and < 1%, INR of 4.84, and activated partial thromboplastin time (APTT) of 49.1 seconds.

The boy was monitored regularly. During examinations, numerous injuries were noted due to his considerable physical activity, repeated episodes of nosebleeds, and recurrent complaints of abdominal, back, and testicular pain. On physical examination, the presence of numerous haemorrhages and ecchymosis localised around the knees, elbows, and fingers of the upper and lower extremities was noted.

At the age of 4 years, the boy was diagnosed with sideropaenic anaemia, caused by chronic blood loss. Laboratory tests showed reduced values of iron (Fe) metabo-

TABLE 1. Test results from 10/11-12-2015

Parameter	Result	Norm
Activated partial thromboplastin time [s]	47.0	25.8–38.6
Prothrombin time [s]	46.7	12–16
International normalised ratio	4.34	0.8–1.2
Thrombin time [s]	19.4	15.5–21.5
Von Willebrand antigen (%)	90	52–154
Antithrombin III (%)	94	85–115
Factor IX (%)	94	60–130
Factor VII (%)	8	70–130
Factor VIII (%)	121	70–130
Factor XI (%)	78	75–112
Factor XII (%)	68	70–130
Fibrinogen [g/l]	2.85	2–4
Von Willebrand factor – activity (%)	92	49–142

TABLE 2. Test results from 21-12-2015

Parameter	Results	Norm
Activated partial thromboplastin time [s]	35.6	25.8–38.6
Prothrombin time [s]	100	12–16
International normalised ratio (INR)	9.92	0.8–1.2
Thrombin time [s]	14.9	15.5–21.5
Factor II (%)	88.9	–
Factor V (%)	99.6	–
Factor VII (%)	1.01	70–130
Factor VIII (%)	85.5	70–130
Factor X (%)	87.3	–
Factor XII (%)	61.6	70–130
Factor IX (%)	83.8	60–130
Factor XI (%)	84.1	75–112

lism parameters: Fe concentration: 29.5 mg/dl (normal 65.0–175.0 mg/dl), ferritin: 10.1 ng/ml (norm 20–200 ng/ml).

The patient was regularly treated with Fe preparations to correct the anaemia. Over several months, it was necessary to administer recombinant FVIIa (Novoseven) at a frequency of 2 to 8 times per month. The boy is under the constant care of the Haematology and Oncology Outpatient Clinic of the University Children's Hospital in Lublin, where he has regular follow-up visits. If necessary, the patient receives Novoseven 0.5 mg at home. The boy's family have been trained and have the necessary knowledge to take actions aimed at reducing bleeding. Each administration of the product is recorded in the home treatment booklet. In addition, in the case of nosebleeds, the boy receives Exacyl orally and topical Emofix and Rinopanteina.

DISCUSSION

The first case of bleeding associated with FVII deficiency was described by Alexander *et al.* [8] in 1951, but the understanding of the pathogenesis and treatment options has changed significantly since then. The aforementioned publication identified SPCA (serum prothrombin conversion accelerator) deficiency as the cause of the coagulation disorder.

Congenital FVII deficiency is an autosomal recessive inherited disorder. By definition, it is a reduction in factor activity below 50% of normal. The gene responsible for the synthesis of this factor is located on chromosome 13 at position q34 and is approximately 12,800 bases long [9]. The structure of the protein is similar to other serine proteases involved in the coagulation process – protein C, factors IX and X [10]. Most patients, despite the presence of pathological mutations, do not exhibit a tendency to bleed in everyday life [11]. This disorder is considered the most common among the rare congenital coagulation defects, accounting for 30% of all such cases [12]. Currently, the prevalence of this condition is estimated at 1/500,000 worldwide [13]. According to data from the National Registry of Congenital Haemorrhagic Disorders, the prevalence of this disorder in Poland can be estimated at approximately 1/174,000 of the population [14]. However, recent data from registries in the UK and Italy suggest that this problem may affect a much larger population of patients, reaching a prevalence comparable to haemophilia B [15].

Genetic diagnosis is hampered by the very wide spectrum of mutations. Currently, the EAHAD Factor VII Gene database contains the description of 1058 cases with 271 genetic variants (<https://f7-db.eahad.org/>) [16]. Additionally, genetic variability is associated with high phenotypic diversity. Studies are being conducted to link specific genotypes to the resulting phenotype, but the results are unsatisfactory [17]. However, it has been confirmed that specific mutations, especially large deletions, impact the decrease in plasma FVII levels, although this does not directly translate into a patient's risk of bleeding [18].

Cases of the acquired form of FVII deficiency have also been described in the literature [7].

The clinical manifestations of FVII deficiency can be highly variable. In most cases, mild mucocutaneous symptoms predominate. Factor levels below 2% increase the risk of severe life-threatening bleeding [19]. The most common are nosebleeds (60%), gingival bleeds (34%), and easy bruising (36%) [3]. In the case we described, despite very low FVII levels, the first symptoms did not appear in the boy until he was 2 years old and these were not severe life-threatening bleeds.

There is no proven correlation between the intensity of bleeding symptoms and FVII levels [3]. Thus, the FVII level cannot determine the choice of appropriate treatment because the parameter alone cannot predict the trend in

bleeding risk. Elements influencing the choice of therapy include the cause of the disease (congenital or acquired), age, the patient's general health, the potential risks associated with the use of certain drugs, and, above all, the choice of treatment depends on the severity of the person's disease [3]. Available therapies include the use of recombinant activated FVII, plasma-derived FVII, fresh frozen plasma or prothrombin complex concentrates [3]. The most commonly used replacement therapy is the administration of genetically modified factor VII (NovoSeven, 15–30 mg/kg b.w./dose), which has good tolerability and efficacy, as well as no risk of pathogen transmission [20]. In the case we presented, treatment was also based on NovoSeven administration. Acute bleeding episodes in individuals with FVII deficiency are effectively managed using fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), activated PCC (aPCC), plasma-derived human FVII (pdFVII), and recombinant activated FVII (rFVIIa). Tranexamic acid is beneficial for treating minor bleeding issues, such as mild menorrhagia, by reducing the duration and intensity of menstrual bleeding. It is also valuable in managing significant bleeding or preventing haemorrhage during major surgeries when used in combination with FFP, aPCC, rFVIIa, and pdFVII. For patients experiencing severe, life-threatening, or frequent bleeding events like CNS bleeding, gastrointestinal bleeding, or hemarthrosis, long-term prophylaxis is usually recommended. However, there are no specific guidelines regarding the dosage, method, or frequency for prophylactic treatment in these patients [12].

CONCLUSIONS

FVII deficiency is a rare coagulation disorder, making each described case important to better understand the clinical spectrum and therapeutic options. The challenge is the lack of correlation between FVII levels and the severity of symptoms that develop. Symptoms may vary in severity among different patients and are often individually variable over time.

The dynamic course of the clinical picture of this factor deficiency makes it a serious clinical challenge that requires constant monitoring. The clinical case we described is an excellent example of the unpredictability of the disease's course, because the first serious bleeding episode did not occur until the child's second year. Since then, the boy has required continuous care and periodic treatment.

DISCLOSURES

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4. Conflicts of interest: None.

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