ABSTRACT

Factor VII (FVII) deficiency is the most common among rare inherited autosomal recessive bleeding disorders. It is a multifaceted disease because of the lack of a direct correlation between plasma levels of coagulation FVII and bleeding manifestations. Clinical phenotypes range from asymptomatic condition—even in homozygous subjects—to severe, life-threatening bleedings (e.g., central nervous system and gastrointestinal bleeding). Menorrhagia is a frequent type of bleeding in FVII deficiency, with a prevalence rate of two in three women aged 10 to 50 years and with a peak prevalence in teenagers. When menorrhagia is observed and once the gynecological causes are excluded, it is important to carry out a hemostasis assessment because, if an anomaly is found, specific treatment can be administered and preventive measures taken. Basic diagnostic work-up includes routine assays, prothrombin level, activated partial thromboplastin time and...

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INTRODUCTION

Coagulation factor VII (FVII) is a blood glycoprotein synthesized by the liver. It intervenes in the exogenous path of coagulation. Congenital FVII deficiency is a very rare deficiency whose prevalence is estimated at 1/500,000 to 1/5,000,000 [1,2,3]. Due to the rarity of the disease, the current knowledge on the clinical profile of affected patients and their treatment is limited [3]. The transmission of this bleeding disorder is autosomal recessive. The clinical expression is very variable and the severity of the hemorrhagic syndrome is not correlated with the residual rates of FVII activity [4]. The clinical picture can be very severe with the early onset of intracerebral hemorrhage, repeated hemorrhosis [5,6] or on the contrary, moderate with cutaneous and mucous haemorrhages (epistaxis, menorrhagia). Menorrhagia is a frequent type of bleeding in FVII deficiency [7] with a prevalence rate of two thirds among women aged 10 to 50 years, with a peak prevalence in teenagers [8,9]. Several therapeutic options are currently available for the treatment of congenital FVII deficiency: recombinant activated factor VII (rFVIIa), plasma-derived FVII, fresh frozen plasma and prothrombin complex concentrates [10]. rFVIIa is the most used replacement therapy, when available. Women with VII deficiency may have heavy and prolonged menstrual bleeding which can sometimes be controlled using antifibrinolytique like tranexamic acid taken during menstruation and hormonal treatments (combined oral contraceptives, levonorgestrel intrauterine devices), in combination or not with rFVIIa [11].

We report the case of a fourteen-and-a-half-year-old girl, who presented menorrhagia of great abundance at the age of thirteen, the exploration of which revealed a congenital deficit in FVII.

2. CASE REPORT

Our report is about a fourteen-and-a-half-year-old girl, the third child of non-consanguineous parents, first admitted to our service when she was thirteen years old. She presented with menorrhagia of great abundance, complicated by anemic syndrome. Blood count tests showed normochromic normocytic anemia, with hemoglobin level at 79 g·L⁻¹, hematocrite at 23.7% and normal rate of platelets (243 10⁹ L⁻¹). Her pelvic ultrasound was normal. The patient’s parents and two siblings have no history of menorrhagia. A general cause has been suspected. A hemostasis assessment was carried out objectifying a prothrombin level at 18% with a normal activated partial thromboplastin time, and the factorial determination revealed a coagulating FVII (FVIIc) at 5% (usual values 70% to 140%). This deficiency in FVII was confirmed on several samples. The search for causes of acquired deficiency (hepatocellular damage, vitamin K deficiency, activation of coagulation, presence of specific FVII inhibitor) was negative. The patient has normal levels of transaminases and of II-IX-X factors. Assessments of antiFVII and of fibrinogen and fibrin degradation products were negative. Replacement therapy with activated recombinant FVII was initiated, with a dose of 30 µg/kg every 6 hours, until bleeding stopped. The patient was prescribed an antifibrinolytic (Exacyl tablets, at 500 mg: 20 mg/kg/day) for use during her menstrual period, and was advised to take oral contraceptive regularly. Follow-up controls showed that the patient no longer presented menorrhagia.

3. DISCUSSION

Coagulation FVII is a plasma vitamin K-dependent serine protease produced by the liver. Blood clotting is initiated by the
interaction between tissue factor (TF) exposed on the vascular lumen upon injury and free circulating activated form (FVIIa) [12]. The FVIIa–TF complex is able to activate factors IX (to FIXa) and X (to FXa), which ultimately induce the formation of a stable fibrin clot [13].

Congenital FVII deficiency was first described in 1951 by Alexander [14]. It is the most common among rare autosomal recessive bleeding disorders. FVII deficiency forms a heterogeneous group on the genotypic and phenotypic levels [15]. It results in a hemorrhagic syndrome that remains the main symptom and is observed in homozygous subjects. Heterozygous subjects are very rarely affected [16,17]. The clinical symptomatology is variable; the deficit can be revealed in the neonatal age by a hemorrhage at the fall of the cord; in childhood by a bleeding during the fall of the baby teeth; and—as is the case of our patient—at puberty by menorrhagia [18]. The deficit can remain unnoticed and only appears in adulthood following a trauma or a surgical procedure, as it can be revealed by hemarthrosis [19]. FVII deficiency is suspected in front of a combination of a decrease prothrombin level and a normal partial thromboplastin time [15,20]. The FVII assay constitutes the method of this screening. To confirm the diagnosis, FVII assay should be repeated at least once (normal values are between 70% and 140%). The correlation between the level of the deficit and the severity of the bleeding is not proven [1,21]. The homozygous form is defined by an abnormally low FVII level of less than 10%, as in the case of our patient. The heterozygous form is defined by levels at the lower limit (70%) of the normal FVII level [18,20]. We proposed genetic screening to parents but they were not interested. Generally, family screening makes it possible to diagnose both homozygous and heterozygous forms, which can remain asymptomatic in the majority of cases until they can manifest as a hemorrhagic syndrome. This screening makes it possible to establish a strategy of prevention and surveillance. The treatment is indicated only in the event of hemorrhagic accidents.

Several therapeutic options are currently available for the treatment of congenital FVII deficiency: rFVIIa, plasma-derived FVII, fresh frozen plasma and prothrombin complex concentrates [10]. rFVIIa is the most used replacement therapy, the recommended dose is 15-30 μg/kg by bolus intra-venous injection every 4-6 hours until haemostasis is achieved [22]. Pharmacokinetic studies in patients with congenital FVII deficiency at steady state have shown a large volume of distribution and a prolonged pharmacodynamics effect of the drug [23]. Excessive menstrual bleeding in a woman with FVII deficiency can be controlled with oral hormonal contraceptive (estroprogestative), hormonal intrauterine device (Mirena®), or antifibrinolytic agents like tranexamic acid taken during menstruation in combination or not with rFVIIa [11].

For our patient, the menorrhagia was so abundant that a decision was made to initiate therapy with activated recombinant FVII immediately after a diagnosis made. When her bleeding stopped, the patient was prescribed an antifibrinolytic for use during her menstrual period, and was advised to take an oral contraceptive regularly. Follow-up controls showed that the patient no longer presented menorrhagia.

4. CONCLUSION

In case of menorrhagia and in the absence of any etiology, a hemostasis assessment must be performed. The case of our patient showed that therapy with rFVIIa [11] followed by antifibrinolytic during the patient’s menstrual period, and regular oral contraceptive is a satisfactory course of treatment for managing menorrhagia.

CONSENT

As per international standard or university standard, patient’s written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.
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