Constitutional Prothrombin Deficiency Revealed by a Family Investigation

Abstract

Congenital prothrombin (factor II) deficiency is an extremely rare inherited coagulation disorder transmitted in an autosomal recessive manner and characterized by wide clinical variability, ranging from mild bleeding manifestations to life-threatening hemorrhage. We report a familial case of severe congenital factor II deficiency diagnosed in the hematology laboratory of the Mohammed V Military Teaching Hospital in Rabat. The index case was a 6-year-old girl born to a second-degree consanguineous marriage, referred for cutaneous bleeding manifestations associated with recurrent knee pain, in a context of prolonged activated partial thromboplastin time and reduced prothrombin time. Coagulation studies revealed an isolated and severe reduction in factor II activity to 3%, with normal levels of the other coagulation factors.

Family investigation identified a similar severe deficiency in both brothers, with variable hemorrhagic manifestations, whereas the parents were asymptomatic and exhibited moderately reduced factor II activity, consistent with a heterozygous carrier state. The combination of clinical and biological findings supported the diagnosis of severe constitutional factor II deficiency, most likely type I. This case highlights the importance of family investigation and consideration of consanguinity in the diagnosis of rare bleeding disorders, and underscores the central role of the laboratory in early identification, patient management, and genetic counseling.

Keywords: Congenital prothrombin deficiency; Factor II; Hereditary coagulopathy; Rare bleeding disorders; Consanguinity; Family investigation.

Introduction

Prothrombin, or factor II, is a plasma glycoprotein synthesized in the liver in the presence of vitamin K and plays a key role in the common pathway of coagulation [1,2]. Congenital prothrombin deficiency is an exceptionally rare coagulation disorder, with an estimated prevalence of approximately one case per two million individuals [3]. It is inherited in an autosomal recessive pattern and is more frequently encountered in regions with a high rate of consanguinity. Clinical manifestations are highly variable, ranging from mild bleeding episodes to severe, potentially life-threatening hemorrhage [4].

Diagnosis relies on a multifactorial approach integrating clinical presentation, personal and family history, laboratory investigations, and molecular analysis [5]. We report a familial case of congenital factor II deficiency diagnosed at the hematology laboratory of the Mohammed V Military Teaching Hospital in Rabat.

Case Report

The index case was a 6-year-old girl, the youngest of three siblings, born to a second-degree consanguineous marriage and originating from Khemisset (western Morocco). She was referred by her pediatrician because of prolonged activated partial thromboplastin time (aPTT) and reduced prothrombin time (PT), associated with cutaneous bleeding manifestations and recurrent knee pain.

Medical history revealed persistent ecchymoses following minor trauma and recurrent hematomas (Figure 1). There was no history of epistaxis, bleeding at umbilical cord separation or vaccination sites, other hemorrhagic manifestations, or medication use.

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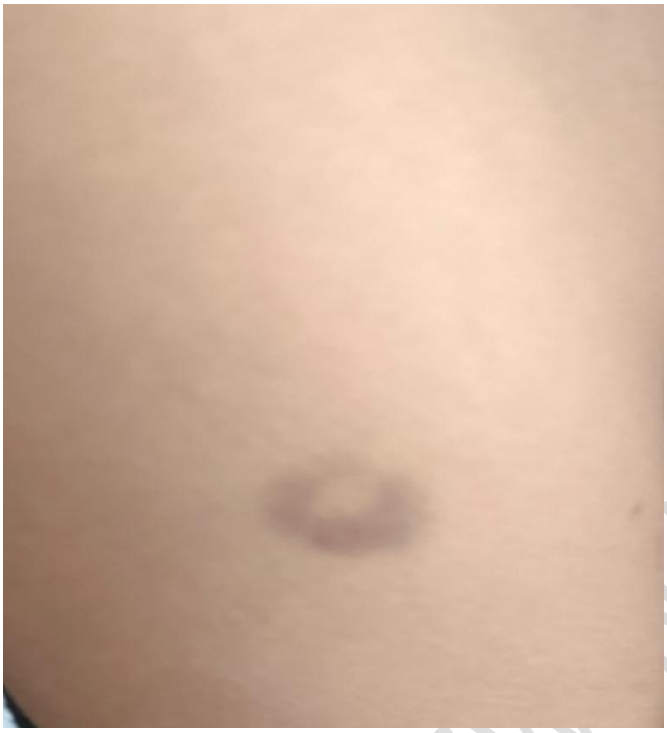

Figure 1. Ecchymotic lesion on the left thigh of the index patient.

Family history indicated no bleeding manifestations in the parents. However, hemorrhagic events were reported in the siblings: the 4-year-old brother experienced severe bleeding during surgery for hypospadias, and the 12-year-old brother had recurrent epistaxis and ecchymoses.

Clinical examination showed ecchymotic lesions on the lower limbs without other bleeding signs. A painful swelling of the right knee without patellar shock and bilateral infracentimetric inguinal lymphadenopathy were also noted. The remainder of the examination was unremarkable.

Laboratory evaluation confirmed prolonged aPTT at 55 seconds (control 36 seconds; ratio 1.5; normal <1.2) and reduced PT at 30% (normal 70–100%). Complete blood count, biochemical tests, and viral serology were normal, and no circulating inhibitors were detected. Specific coagulation factor assays revealed an isolated and severe reduction in factor II activity to 3%, with normal activity of all other coagulation factors, including von Willebrand factor. These findings supported the diagnosis of severe congenital factor II deficiency.

Family Investigation

Given the diagnosis in the index patient, the hemorrhagic history within the sibship, and parental consanguinity, a family investigation was conducted in both brothers and parents. The 4-year-old brother showed prolonged aPTT, reduced PT, and markedly decreased factor II activity at 3% (Table 1), with a history of significant surgical bleeding. The 12-year-old brother presented similar abnormalities, with factor II activity at 4% (Table 1), and reported recurrent epistaxis and spontaneous or post-traumatic ecchymoses (Figure 2).

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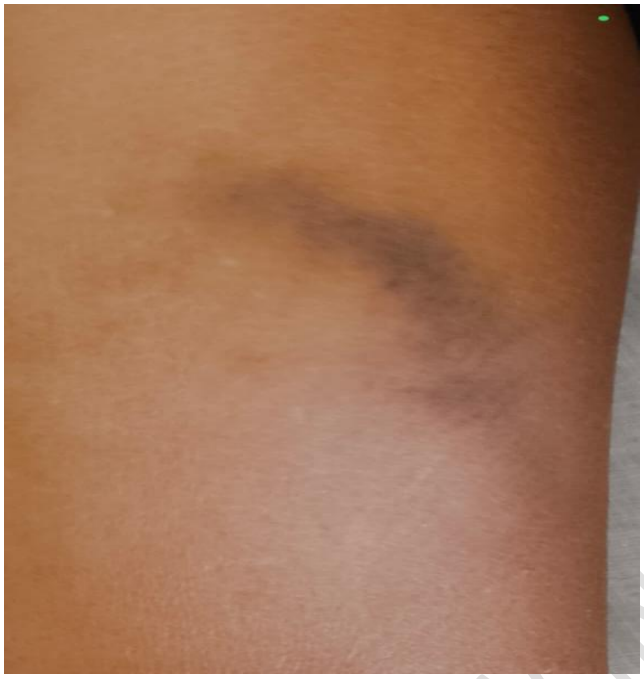

Figure 2. Large ecchymotic lesion on the right thigh of the 12-year-old brother.

In contrast, both parents had normal aPTT and PT values but moderately reduced factor II activity, around 50% (Table 1), and were clinically asymptomatic, consistent with a heterozygous carrier state. No specific treatment was initiated for the children; fresh frozen plasma was reserved for the management of bleeding episodes.

Table 1. Biological results of the family investigation.

Parameter	Father	Mother	Brother 1	Brother 2
PT (%)	85.0 %	85.0 %	**26.0 %**	**34.0 %**
aPTT ratio	0.9	0.9	**1.6**	**1.4**
Factor II (%)	**51.0 %**	**58.0 %**	**3.0 %**	**4.0 %**
Factor V (%)	82.0 %	98.0 %	63.0 %	99.0 %
Factor VIII (%)	212.0 %	170.0 %	217.0 %	237.0 %
Factor IX (%)	148.0 %	126.0 %	81.0 %	91.0 %
VWF Ag(%)	-	-	127.0 %	189.0 %

Discussion

Prothrombin is a vitamin K-dependent glycoprotein synthesized in the liver and encoded by the *F2* gene located on the short arm of chromosome 11. The gene encodes a 622-amino-acid pre-propeptide that undergoes several post-translational modifications to yield mature prothrombin, which is secreted into the plasma.

Mature factor II circulates at a concentration of approximately 0.1 mg/mL and has a half-life of about 60 hours. It is composed of four domains connected by three flexible segments: an N-terminal

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γ-carboxyglutamic acid (Gla) domain, two kringle domains (kringle 1 and kringle 2), and a serine protease catalytic domain consisting of A and B chains linked by a disulfide bond. The catalytic site is located within the B chain and is situated in a deep pocket surrounded by flexible loops that regulate substrate access.

In plasma, prothrombin exists in equilibrium between two conformations: a predominant closed form (~80%), in which the kringle-1 domain shields the catalytic pocket, and a minor open form (~20%), in which the catalytic site is exposed, allowing potential receptor interactions or altered proteolytic susceptibility [2]. The Gla domain contains ten γ-glutamyl residues that are carboxylated by γ-glutamyl carboxylase in the presence of vitamin K, a modification essential for calcium binding and anchoring of prothrombin to anionic phospholipid surfaces of activated platelets [6].

Within the coagulation cascade, prothrombin plays a pivotal role as the precursor of thrombin (factor IIa), a key enzyme with both procoagulant and anticoagulant activities [7]. Activation by factor Xa in the presence of phospholipids, calcium, and factor Va generates thrombin, which converts soluble fibrinogen into insoluble fibrin and amplifies coagulation by activating factors V, VIII, and XIII and stimulating platelet aggregation, while also exerting anticoagulant effects through the thrombomodulin–protein C pathway. In addition, thrombin has several non-hemostatic biological functions, including roles in cell proliferation, chemotaxis, tissue repair, and angiogenesis [7,8].

Factor II deficiency may be congenital or acquired. Acquired forms can result from vitamin K deficiency, liver disease, or, more rarely, lupus anticoagulant–hypoprothrombinemia syndrome associated with the presence of a lupus anticoagulant [9]. Congenital factor II deficiency is an autosomal recessive disorder caused by various mutations in the *F2* gene; more than 60 mutations have been described, affecting all domains of the prothrombin molecule [5,7].

Congenital prothrombin deficiencies are currently classified into three types: type I (true hypoprothrombinemia), characterized by reduced prothrombin activity and antigen levels and typically associated with significant bleeding; type II (dysprothrombinemia), a qualitative defect with markedly reduced activity despite normal or near-normal antigen levels and variable bleeding tendency; and type III (dysprothrombinemia associated with thrombosis), characterized by antithrombin resistance and an increased thrombotic risk without bleeding manifestations [10].

Clinically, factor II deficiency usually presents with mucocutaneous bleeding, menorrhagia, hematomas, hemarthroses, and prolonged bleeding after dental extraction or trauma, while life-threatening hemorrhages such as intracranial or gastrointestinal bleeding are rare [5,9,11]. In most cases, there is a strong correlation between clinical severity and residual factor II activity, with levels below 10% generally associated with severe bleeding [12]. Complete absence of prothrombin is incompatible with life, and even severely affected homozygous patients retain minimal residual activity [11].

Diagnosis of congenital coagulation factor deficiencies relies on a comprehensive approach combining clinical evaluation, family history, laboratory screening tests, and molecular analysis. Prolongation of aPTT associated with reduced PT suggests a defect in the common pathway and warrants specific assays of factors I, II, V, and X [5,13]. Confirmation of factor II deficiency requires demonstration of isolated reduction in factor II activity, after exclusion of acquired causes and inhibitors using mixing studies [4,9,13]. Measurement of prothrombin antigen levels is essential for proper phenotypic classification, and molecular analysis by direct sequencing provides definitive diagnosis and facilitates genetic counseling [5].

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In the present case, the combination of severe factor II deficiency in all siblings and moderate deficiency in asymptomatic parents supports an autosomal recessive inheritance pattern, with heterozygous parents and homozygous affected children. Second-degree parental consanguinity represents a major risk factor explaining the occurrence of severe disease within the sibship. Although antigenic assays were not performed, the very low factor II activity levels (3–4%) are consistent with type I deficiency. From a clinical standpoint, phenotypic distinction has limited therapeutic relevance, as management in both types aims to restore functional circulating prothrombin using prothrombin complex concentrates or fresh frozen plasma, given the absence of purified factor II concentrates [14,15,17].

Conclusion

Congenital prothrombin deficiency is an extremely rare autosomal recessive bleeding disorder whose severe forms may be life-threatening. Diagnosis requires a rigorous approach combining clinical findings, targeted coagulation studies, and careful assessment of family history, with consanguinity being a key indicator of a constitutional etiology. Family investigation is essential to confirm the diagnosis, identify asymptomatic carriers, and optimize patient management and genetic counseling, particularly in populations with a high prevalence of consanguinity.

Ethical Approval and Consent

Written informed consent was obtained from the parents.

Conflict of Interest

The authors declare no conflict of interest.

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