

Umbilical bleeding revealing congenital factor XIII deficiency in a newborn: A case report and literature review

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Abstract

Factor XIII Deficiency is a rare congenital coagulopathy, frequently revealed during the neonatal period by unusual bleeding manifestations, particularly umbilical bleeding, while routine coagulation tests are often normal, leading to delayed diagnosis. We report the case of a female neonate born to first-degree consanguineous parents, admitted on day 15 of life for umbilical bleeding occurring at the time of cord separation. Initial clinical examination was unremarkable apart from active umbilical bleeding. Routine coagulation investigations were within normal limits. The diagnosis was confirmed by a factor XIII activity level of 6%. The clinical course was marked by recurrent post-traumatic bleeding episodes, managed with fresh frozen plasma and tranexamic acid in the absence of specific replacement therapy. Factor XIII deficiency should be suspected in any neonate presenting with umbilical bleeding despite normal routine coagulation tests. The diagnosis relies on specific factor XIII assays and is essential for appropriate therapeutic management. Limited access to replacement therapy may delay prophylactic treatment and necessitate an on-demand therapeutic approach.

Keywords: Factor XIII; Neonate; Rare bleeding disorder; Umbilical hemorrhage; Consanguinity; Congenital coagulation factor deficiency

1. Introduction

The coagulation factor XIII (FXIII) plays a crucial role in the final phase of coagulation by ensuring fibrin clot stabilization and resistance to fibrinolysis. Clinically, severe forms are usually revealed early in life, particularly during the neonatal period, most commonly by umbilical bleeding, which is reported in nearly 80% of cases, as well as by potentially life-threatening intracranial hemorrhage. The diagnosis is often delayed because routine coagulation tests are usually normal and therefore relies on specific FXIII assays [1]. In this context, we report a case of neonatal umbilical bleeding revealing congenital factor XIII Deficiency, illustrating the diagnostic challenges and highlighting the importance of early management to prevent severe hemorrhagic complications.

2. Case presentation

We report the case of a female neonate born at term from a well-monitored pregnancy with no notable complications. She was admitted to the neonatology department on day 15 of life for umbilical bleeding. The family history was notable for first-degree parental consanguinity, the death of a sibling at day 38 of life in a hemorrhagic context following traditional uvulectomy, and a 6-year-old sister who had presented with mild neonatal umbilical bleeding that resolved favorably with symptomatic treatment. On admission, the neonate was in good general condition, with stable hemodynamic and respiratory status. Abdominal examination revealed traces of blood without active bleeding. No

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other hemorrhagic manifestations were observed, particularly no ecchymoses or cutaneous-mucosal bleeding. Initial management consisted of hospitalization and placement of a peripheral venous line. Laboratory investigations showed a hemoglobin level of 17 g/dL, which subsequently decreased to 14.6 g/dL and then to 12.3 g/dL, with a white blood cell count of $10,210/\text{mm}^3$ and a platelet count of $326,000/\text{mm}^3$. Routine coagulation tests revealed a prothrombin time of 96% and a normal activated partial thromboplastin time. Liver, renal, and infectious workups were unremarkable. Specialized investigations confirmed congenital factor XIII Deficiency with a factor XIII level of 6%. During hospitalization, the clinical course was marked on the third day by minimal recurrent umbilical bleeding requiring transfusion of fresh frozen plasma. The outcome was favorable, with cessation of bleeding and clinical stabilization, allowing discharge after five days of hospitalization. During follow-up, the child experienced several hemorrhagic episodes following minor trauma, mainly consisting of ecchymoses and soft tissue hematomas. Some episodes required hospital management with fresh frozen plasma transfusion because specific factor XIII concentrate was unavailable. No prophylactic treatment could be initiated because of the unavailability of specific factor XIII replacement therapy in our setting. Management therefore relied on an on-demand therapeutic approach combining fresh frozen plasma and tranexamic acid, with an overall favorable outcome.

3. Discussion

Congenital Factor XIII Deficiency is a rare coagulopathy, with an estimated incidence ranging from 1 to 3 cases per million inhabitants, and is more frequently reported in populations with a high rate of consanguinity [1]. In our case, parental first-degree consanguinity and the family history of hemorrhagic events strongly support an autosomal recessive mode of inheritance, as previously described in the literature [1,2]. Factor XIII is a pro-transglutaminase involved in the final phase of coagulation. It is activated by thrombin in the presence of calcium ions, leading to dissociation of the B subunits and generation of the active enzyme FXIIIa, which covalently cross-links fibrin and alpha-2-antiplasmin, thereby strengthening clot stability and protecting it against fibrinolysis [2]. Deficiency of FXIII results in the formation of unstable clots, explaining the occurrence of severe bleeding manifestations, particularly umbilical cord bleeding, intracranial hemorrhage, and muscular or subcutaneous hematomas [3]. Congenital FXIII deficiency most commonly results from autosomal recessive mutations in the F13A1 gene and, less frequently, in the F13B gene, leading either to quantitative deficiency of the A subunit or qualitative impairment of its enzymatic activity [4]. Clinically, factor XIII deficiency is mainly characterized by neonatal umbilical bleeding, reported in nearly 80% of severe cases, as well as spontaneous intracranial hemorrhage (25–30% of cases), cutaneous or muscular hematomas, hemarthrosis, post-traumatic or postoperative bleeding, and mucosal or gastrointestinal hemorrhage [2,5,7]. The disease may be revealed during the neonatal period, particularly by umbilical bleeding as observed in our patient, after invasive procedures such as circumcision, or later in life. This mode of presentation is highly suggestive, especially when it occurs in the absence of abnormalities in routine coagulation tests. Indeed, standard coagulation investigations are usually normal because FXIII acts downstream from clot formation [2,5,7]. In our patient, a prothrombin time of 96% associated with a normal activated partial thromboplastin time was consistent with this characteristic biological profile, which may contribute to delayed diagnosis. The diagnosis relies on specific measurement of FXIII activity. Antigenic assays evaluating the A and B subunits help distinguish between different forms of deficiency. Recent advances, including automated assays and chromogenic methods, have improved the detection of low FXIII levels and therapeutic monitoring. Genetic analysis of F13A1 and F13B confirms the diagnosis and enables appropriate family counseling [2,5]. In our patient, a FXIII level of 6% corresponded to a moderate deficiency at the borderline of severe forms; however, the neonatal presentation with umbilical bleeding reflected a severe hemorrhagic phenotype. From a therapeutic perspective, FXIII is characterized by a long plasma half-life of approximately 9 to 14 days, allowing the implementation of effective prophylactic strategies. Prophylaxis is recommended in severe forms because of the high risk of life-threatening hemorrhage, particularly intracranial bleeding, which remains the leading cause of mortality [8]. The standard treatment consists of prophylactic administration of recombinant factor XIII (rFXIII-A) at a dose of 35 IU/kg every four weeks, maintaining protective trough levels and effectively preventing hemorrhagic episodes. Data from clinical trials and real-world studies have demonstrated its excellent efficacy and safety profile, including in pediatric patients [9,10]. In cases of active bleeding, curative administration of factor XIII is required at doses of 20–40 IU/kg for plasma-derived factor XIII concentrate (pFXIII) and 35 IU/kg for recombinant factor XIII (rFXIII). Fresh Frozen Plasma remains a therapeutic alternative at a dose of 10–20 mL/kg. Antifibrinolytic agents such as Tranexamic Acid may be used as adjunctive therapy, particularly in mucosal bleeding [2,8]. In our setting, the unavailability of factor XIII concentrate prevented the initiation of prophylactic therapy, resulting in an on-demand treatment strategy based on fresh frozen plasma and tranexamic acid. This situation highlights the limitations of management in resource-limited settings and underlines the importance of improving access to specific therapies in order to prevent severe hemorrhagic complications.

4. Conclusion

Congenital factor XIII Deficiency should be suspected in cases of neonatal umbilical bleeding, particularly in the setting of consanguinity, even when routine coagulation tests are normal. The diagnosis relies on specific investigations and is essential for the initiation of effective prophylactic therapy aimed at preventing severe hemorrhagic complications, especially intracranial bleeding. Improving access to replacement therapy remains a major challenge in resource-limited countries.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

Ethical approval was not required for this case report according to institutional policy.

Statement of informed consent

The case report was fully anonymized. No identifiable personal information or images are included. According to institutional policy, formal written informed consent was not required for publication of this anonymized case report.

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