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– CASE REPORT –

Unexpected Bleeding Normal Coagulation Tests: Congenital Factor XIII Deficiency

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Abstract

Congenital factor XIII deficiency is a very rare bleeding disorder, which affects one in 1-2 million patients globally and is a difficult disease to diagnose, because of the normality of routine coagulation tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels. This coagulopathy is either congenital or acquired, but most documented cases are congenital, being caused by the mutation of F13A1 gene which encodes the A subunit of the factor XIII heterotetramer (A2B2 complex).

The clinical manifestations of factor XIII deficiency consist in uncontrolled bleeding, poor wound healing, even miscarriages in young women and intracranial bleeding.

Management of this deficiency is based on replacement therapy, including factor XIII concentrates (both plasma-derived and recombinant), cryoprecipitate and fresh frozen plasma, each having specific indications and adverse reactions.

The clinical case presented above illustrates a young female with a history of multiple episodes of spontaneous hemoperitoneum, a severe adverse reaction to fresh frozen plasma (TRALI) and a delayed factor XIII deficiency diagnosis.

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Introduction

Factor XIII deficiency is a very rare but critical coagulation disorder, affecting 1 in 1-2 million patients and its late diagnosis can be life-threatening, as it can develop unexpected bleeding in spite of normal routine coagulation tests (PT, aPTT, thrombin time). This happens because factor XIII acts after fibrin formation to stabilize the clot, and its deficiency does not affect the initial steps measured by standard assays. Thus, clinical presentation shows significant bleeding—such as umbilical stump bleeding, delayed soft tissue or postoperative haemorrhage. This is why screening neonates for congenital factor XIII deficiency results are false-negative and guidelines recommend the quantitative activity assay to help diagnose patients.

The more severe the factor XIII deficiency, the more striking the clinical manifestations, including intracranial

hemorrhage, poor wound healing, and recurrent miscarriages in women of childbearing age. (1–4)

Factor XIII circulates in plasma as a heterotetramer composed of two catalytic A subunits and two non-catalytic (carrier) B subunits (FXIII-A_2B_2). The A subunit, encoded by the F13A1 gene, provides the enzymatic activity required for cross-linking fibrin and other proteins, thereby conferring mechanical stability and resistance to fibrinolysis. The B subunit, encoded by the F13B gene, acts as a carrier, protecting the A subunit from proteolytic degradation and facilitating its persistence in circulation. Deficiency of the A subunit leads to severe, lifelong bleeding, poor wound healing, and recurrent miscarriage, while the B subunit deficiency is typically a milder type, due to its non-catalytic role. Both subunits are required for normal plasma levels, as the A subunit stabilizes the B subunit and the other way around. (5)

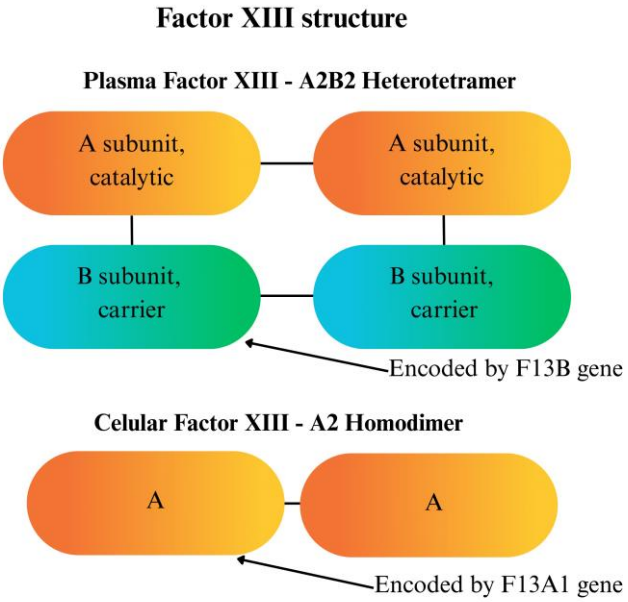

Figure 1. *Factor XIII structure: plasmatic and cellular. Plasma form: A_2B_2 heterotetramer, with F13A1 (A subunits) and F13B (B subunits). Cellular form: A_2 homodimer (only catalytic A subunits).*

The treatment in factor XIII deficiency is permanent and consists in replacement therapy. The first line of treatment are factor XIII concentrates (plasma-derived or recombinant) and is to be used in both congenital and acquired forms of this disease. The plasma-derived factor XIII concentrate contains both subunits (A and B), whereas the recombinant factor XIII replaces only the A subunit. For the diagnosis of congenital factor XIII-A deficiency, recombinant factor XIII concentrate is effective, having the role of increasing A subunit and stabilizing B subunit levels in plasma. For congenital factor XIII-B deficiency, the plasma-derived concentrate is preferred, as the latter does not address the absence of the B subunit. Therefore, in order to optimize patient care, it is essential to identify which subunit of factor XIII is affected, as the catalytic A subunit is encoded by the F13A1 gene and the carrier B subunit by the F13B gene; this distinction has significant implications for both diagnostic evaluation and therapeutic strategy. Other alternatives for treatment are cryoprecipitate and fresh frozen plasma, but they are less efficient than factor XIII concentrates and they are to be used when concentrations of any type are not available. Both cryoprecipitate and fresh frozen plasma contain factor XIII but in lower levels when compared to factor XIII concentrates. Their indication is in acute bleeding and short-term prophylaxis, whereas the factor XIII concentrates are a better treatment option for long-term prophylaxis. There are also numerous risks and adverse reactions associated with cryoprecipitate and fresh frozen plasma, varying from transfusion-transmitted infections, anaphylactic reactions and allergies to transfusion-related acute lung injury (TRALI), which is a critical emergency. (6–9)

However, there is limited data on how to facilitate the diagnosis, because the routine coagulation tests are normal in patients with congenital factor XIII deficiency and the traditional clot solubility tests only detect the severe deficiencies (under 5% activity of factor XIII), leaving out the milder cases or the clinically silent ones. The lack of screening tests and protocols is an important matter for clinicians which leads to delayed or even missed diagnoses.

Evidence regarding replacement therapy remains also scarce. There are a few clinical studies developed on patients who received recombinant or plasma-derived factor XIII concentrates, but the long-term impact on the human body is insufficiently investigated.

Nevertheless, another knowledge gap regarding congenital factor XIII deficiency is the absence of the multicenter and prospective studies, alongside standard criteria for screening, laboratory tests and diagnosis, to better understand and manage this disease.

Clinical case

We report the case of a 23-year-old woman with short stature (nanism phenotype), one previous childbirth, a regular menstrual cycle, and no history of miscarriages. She has no cognitive or psychiatric impairment. Her past medical history includes pulmonary tuberculosis, appendectomy, surgery for extradural spinal haematoma, and a femoral fracture. Since childhood, she has experienced recurrent episodes of spontaneous hemoperitoneum.

Her family history is relevant for the father's death at the age of 40 due to cerebrovascular accident.

Since childhood, the patient had recurrent spontaneous hemoperitoneum, extensive haematomas and episodes of prolonged haemorrhage, despite repeatedly normal routine coagulation tests. She experienced six episodes of hemoperitoneum in total, the most recent occurring after giving birth to a healthy child, a clinical picture highly suggestive for congenital factor XIII deficiency. She was eventually diagnosed with congenital factor XIII deficiency at the age of seventeen, with factor XIII activity <5% and an A-domain deficit (3.4%, reference range 47–137%), confirming severe deficiency. According to international guidelines, first-line therapy should have consisted in factor XIII concentrate. However, as this medication was not available in Romania, she received fresh frozen plasma (one unit every two weeks). Under this regimen, she continued to develop haematomas after minimal trauma, until she developed transfusion-related acute lung injury (TRALI) in November 2024.

Subsequently, she was admitted to hospital with severe pain in the left thigh, marked swelling, and functional impairment. The haematoma was triggered by the minor mechanical stress of sitting in a rocking chair, underscoring the extreme bleeding tendency associated with her condition. CT imaging revealed a heterogeneous haematoma measuring 100 × 55 × 130 mm within the posterior thigh muscle compartment, consistent with a major spontaneous intramuscular haemorrhage.

Therefore, treatment with recombinant factor XIII concentrate was initiated, administering 40IU/kg every 28 days, aiming to maintain factor XIII activity between 5% and 20% and, also, pharmacokinetic assessment was performed before and after the first infusion. Pre-infusion FXIII activity was 49.3% (reference range: 75–155%). Following administration of 40IU/kg, activity levels exceeded the measurable range of the assay at both 30 minutes and 1 hour post-infusion. One day post-infusion, the factor XIII activity declined from 399% to 123.8% in a few hours, leading to a value of 94% 5 days post-infusion. Taking into consideration drug dose adjustment regimen, treatment was continued with 30IU/kg every 28 days. The following activity measurements demonstrated a gradual decline over time, prompting dose escalation to 35IU/kg every month.

Besides functional activity, factor XIII antigen (reflecting plasma protein concentration, particularly of the A subunit) was also measured throughout treatment cycles, showing normal values, demonstrating the effectiveness of recombinant factor XIII concentrate therapy.

The patient has now completed seven months of treatment without any adverse reactions, not even during the initial infusion. Prophylactic medication was systematically administered before each cycle, in line with guidelines and the Summary of Product Characteristics (SmPC). During every hospital admission, factor XIII antigen and routine coagulation tests were measured, with the latter consistently remaining within normal limits. Dynamic monitoring indicated a half-life of approximately 28 days for recombinant factor XIII, with antigen levels showing a predictable decline just prior to the next cycle.

Clinically, the patient has shown an excellent evolution: no further episodes of haemoperitoneum or spontaneous haematomas, and no prolonged bleeding after minor injuries. The most important aspects of her progress are the significantly improved quality of life and the ability to carry out daily activities without any restrictions.

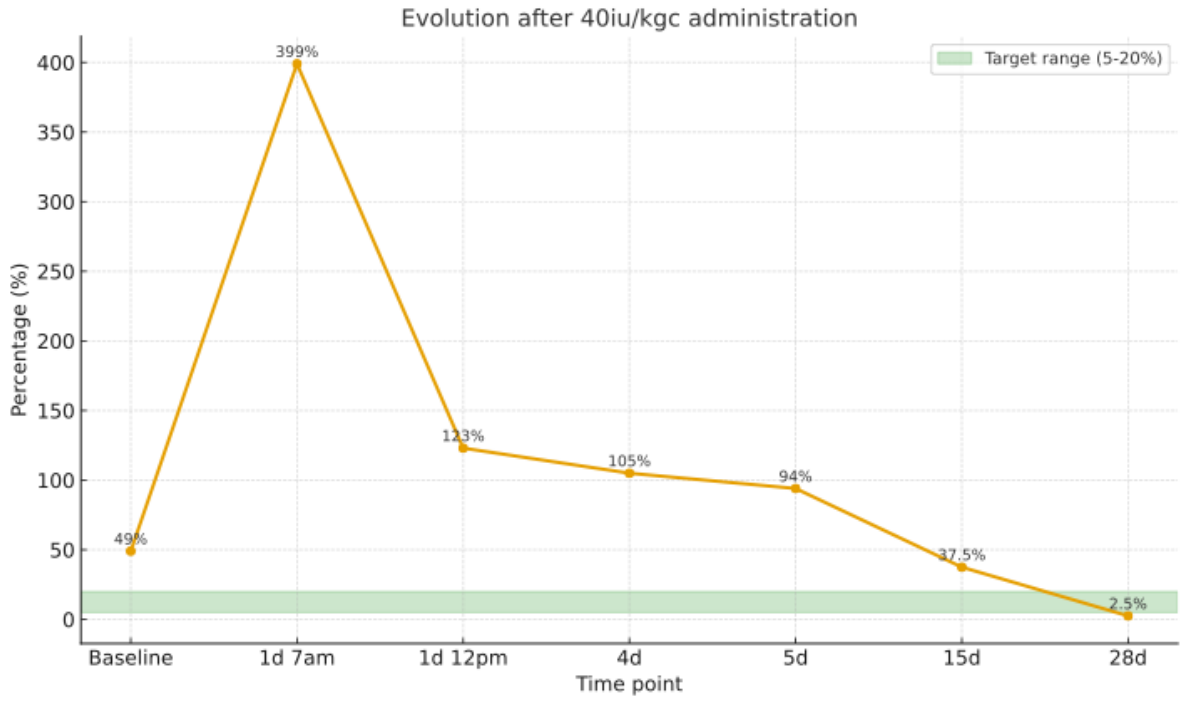

Figure 2. *The graph shows percentage evolution following administration of 40 IU/kgc. Levels rise sharply post-infusion, peaking at 399% at 24h, then gradually decrease to 123% (12h), 105% (day 4), and 94% (day 5). At day 15, values decline to 37.5%, and by day 28 they fall to 2.5%, prior to the next cycle. The shaded area indicates the target range of recombinant factor XIII activity (5–20%), which is consistently exceeded during the early phase and undercut by the end of the cycle.*

Discussion

When comparing to literature finds, it was also stated in a clinical study of 13 patients who also received recombinant factor XIII concentrate on days 0, 28 and 56, that pharmacokinetic (PK) tests were run and maximum factor XIII activity was 87.7% at 1.72 hours post-infusion. Nevertheless, it declined to a minimum of 5% with a half-life of 6.6 days. In the presented clinical case, the factor XIII antigen measured exceeded the capacity of the machine 30 minutes and one hour post-infusion. One day after infusion, factor XIII antigen was measured at 399%, with a normal range between 75-150%. During the following four days, the factor XIII declined, with values ranging from 123% to 94%. (10)

Another clinical study conducted in 41 patients who received plasma-derived concentrate showed that no patient presented spontaneous bleedings, no viral transmissions were observed, and no thromboembolism-related events occurred. So, both factor XIII concentrates (plasma-derived and recombinant) are well-tolerated by patients. (11)

Conclusion

Congenital factor XIII deficiency, even though it is a rare disorder, should be taken into consideration when encountering patients with severe and inexplicable bleeding and normal routine coagulation tests. The earlier it is recognised and diagnosticated, the less frequent the risks of life-threatening complications appear.

Routine coagulation tests are not sufficient to diagnose the factor XIII deficiency, as it is necessary to evaluate factor's activity and antigen levels, along with genetic testing.

The management plan includes different types of replacement therapies, each with their adverse reactions, but it is necessary to be informed about all lines of treatment, especially when cryoprecipitate and fresh frozen plasma are potentially more dangerous.

The previously presented case illustrates how important and life-saving an early diagnosis can be and, also, the need of continuous monitoring of therapeutic response in patients with congenital factor XIII deficiency. The

sooner adequate therapy is initiated, the greater the improvement in the patient's daily life.

Ethics Statement and Conflict of Interest Disclosures

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Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by the patient in this study.

Conflict of interest: No known conflict of interest correlated with this publication.

Availability of data and materials: The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interests: The authors declared that they have no competing interests.

The use of generative AI and AI-assisted technologies: The authors did not use in this article generative AI and AI-assisted technologies.

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