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Relato de Caso

Factor XIII deficiency, a rare coagulopathy: case reports

Deficiência do fator XIII, uma coagulopatia rara: relato de casos

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RESUMO

Introduction: Hereditary Factor XIII (FXIII) deficiency is a rare autosomal recessive hemostatic disorder with an estimated incidence of one case per two million individuals and a higher prevalence in descendants of consanguineous relationships. Possible clinical manifestations include intracranial hemorrhage, umbilical cord bleeding at birth, hematoma, spontaneous abortions, and menometrorrhagia. **Objective:** To highlight the peculiarities of this hemostatic disorder, as well as the recommended management. **Case Report:** The authors describe two cases of FXIII deficiency with different hemorrhagic manifestations. Case 1 presented extensive spontaneous hematoma in the right thigh, while Case 2 had umbilical cord bleeding at birth and intracranial hemorrhage, requiring hemotherapy support. Both patients had normal results in screening laboratory tests for coagulation disorders. Coagulation factor serum levels and diagnostic assessments identified mild Factor XIII deficiency in Case 1 and severe deficiency in Case 2. The patient in Case 1 is under regular control and follow-up, while the patient in Case 2 is on a monthly prophylactic regimen with FXIII infusion. **Conclusion:** The diagnosis of FXIII deficiency in patients with significant bleeding should be considered if screening coagulation tests are normal. The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis has established an algorithm for laboratory diagnosis and identification of different forms of FXIII deficiency. Quantitative determination of FXIII activity, antigenic assays, and molecular studies are necessary.

Palavras-chave: Factor XIII Deficiency; Coagulation Protein Disorders; Blood Coagulation Disorders, Inherited; Factor XIII.

RESUMO

Introdução: A deficiência hereditária do Fator XIII (FXIII) é uma rara desordem autossômica recessiva da hemostasia, com uma incidência estimada de um caso a cada dois milhões de pessoas e uma maior prevalência em descendentes de relacionamentos consanguíneos. Possíveis manifestações clínicas incluem: hemorragia intracraniana, sangramento do cordão umbilical no nascimento, hematoma, abortos espontâneos e menometrorragia. **Objetivo:** Ressaltar as particularidades desse distúrbio hemostático, assim como o manejo preconizado. **Relato de caso:** Os autores descrevem dois casos de deficiência de FXIII com diferentes manifestações hemorrágicas. O Caso 1 apresentou extenso hematoma espontâneo na coxa direita, enquanto o Caso 2 apresentou sangramento do cordão umbilical ao nascer e hemorragia intracraniana, necessitando de suporte hemoterápico. Ambos os pacientes apresentavam resultados normais nos testes laboratoriais de triagem para distúrbios de coagulação. As dosagens séricas de fatores de coagulação e de diagnóstico identificaram deficiência leve do Fator XIII no Caso 1 e grave no Caso 2. O paciente do Caso 1 está sob controle e acompanhamento regular, enquanto o paciente do Caso 2 está em regime profilático mensal com infusão de FXIII. **Conclusão:** O diagnóstico de Deficiência de FXIII em pacientes com sangramento importante deve ser considerado se os testes de coagulação de triagem forem normais. O Comitê Científico e de Padronização da Sociedade Internacional de Trombose e Hemostasia estabeleceu um algoritmo para o diagnóstico laboratorial e identificação de diferentes formas de deficiência FXIII. A determinação quantitativa da atividade do FXIII, ensaios antigênicos e estudos moleculares são necessários.

Key-words: Deficiência do Fator XIII; Transtornos de Proteínas de Coagulação; Transtornos Herdados da Coagulação Sanguínea; Fator XIII.

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INTRODUCTION

Hereditary Factor XIII Deficiency (FXIIID) is a rare disorder of hemostasis, autosomal recessive, and, with a prevalence of about one per 1 million people, with a higher prevalence in descendents of consanguineous relationships.[1-3] Data from the Ministry of Health publication indicates that Brazil had 96 cases of FXIIID registered in 2022, a value that corresponds to a 2.97 % prevalence of rare coagulopathies in the country.[4] In the previous year (2021), Brazil had 90 cases of FXIIID documented, representing a prevalence of 3.02% for rare coagulopathies in the country.[5] It is crucial to underscore that, in this calculation, individuals diagnosed with hemophilia and von Willebrand disease have been excluded. FXIIID can present significant hemorrhagic manifestations – intracranial hemorrhage (IH), umbilical cord bleeding, hematoma, hemarthrosis, menorrhagia or minor bleeding, whose severity is inversely proportional to the individual plasma level of FXIII and determines repeat abortions.[6] Umbilical stump bleeding is very suggestive of this clotting disorder, occurring in 80% of cases and IH is the main cause of death.[2]

Coagulation Factor XIII (FXIII) is a pro transglutaminase formed by two A subunits (FXIII-A) and two B subunits (FXIII-B) that circulates as a heterotetramer (FXIII-A2B2), catalyzing the formation of cross-links between the monomers of fibrin and between α2-antiplasmin and fibrin.[1-3] FXIII-A is produced in the bone marrow, while FXIII-B is produced by hepatocytes.[1] Activated FXIII promotes stabilization and protection of newly formed fibrin against premature fibrinolysis, with an extremely relevant role in hemostasis, pregnancy maintenance, wound healing, and angiogenesis.[2,6]

FXIIID is due to a mutation in the gene that encodes the A subunit of FXIII or the B subunit. FXIII-A deficiency is more frequent and severe.[2] Over 200 genetic mutations have been recognized since the initial instance of inherited FXIII deficiency was documented. A newly discovered and probably pathogenic mutation in the F13A1 gene was reported, expanding the range of gene mutations associated with inherited FXIII deficiency.[7]

The diagnosis of FXIIID is difficult and complex, characterized by the normality of all screening coagulation tests (fibrinogen, prothrombin Time – PT, activated thromboplastin time – aPTT, thrombin time – TT, and bleeding time-TS) regardless of the severity of the hemorrhage, since FXIII acts in the final phase of fibrin formation and routine laboratory evaluation does not detect changes in the final phase of coagulation. The clinical hypothesis for FXIIID includes a well-detailed anamnesis with family history and physical examination, in addition to a healthcare professional familiar with rare bleeding disorders.[6,8] Diagnostic confirmation is performed with specific qualitative and quantitative FXIII tests, antigenic assays, and molecular and genetic tests.[6,9,10]

Therapeutic management is based on hemotherapy support with blood components that contains FXIII (fresh frozen plasma and cryoprecipitate) and recombinant FXIII concentrate, the latter being the most recommended. The plasma concentration of FXIII required for preventing spontaneous bleeding varies between 5% and 30%. The replacement of FXIII is recommended in patients with severe FXIII deficiency at the time of diagnosis, typically those who are homozygous with a serum FXIII level below 1%. Due to the high risk of associated intracranial hemorrhage, primary prophylaxis for this event is advised through regular FXIII replacement, aiming to maintain FXIII levels between 1% and 4%. The interval between transfusions should be 4–6 weeks, at a dose of 10 IU/kg–20 IU/kg. In the unavailability of FXIII concentrate, treatment can be carried out with cryoprecipitate, one bag per 10 kg–20 kg of body weight every 3 or 4 weeks, or alternatively, with fresh frozen plasma at a dose of 10 mL/kg every 3 to 4 weeks. Additionally, patients with FXIII levels < 4 IU/dL who have experienced a severe bleeding episode, particularly intracranial hemorrhage, also have an indication for secondary prophylaxis with FXIII replacement.[6]

Other situations in which FXIII replacement is recommended include during acute bleeding episodes and before surgeries (with replacement continuing until complete healing of the injury).[6] The recommended doses of FXIII concentrate for each situation and the duration of such measures are outlined in Table 1.

Pregnancy in women with FXIII deficiency also requires regular replacement of this factor, immediately after the diagnosis of pregnancy. In this case, FXIII levels should be mantained between 3 IU/dL and 10 IU/dL. This corresponds to an approximate dose of 250 IU of FXIII concentrate per week in the first 22 weeks of gestation. From then on, the dose should be increased to 500 IU per week until delivery. At the time of delivery, aiming to prevent hemorrhagic complications, the recommended dose becomes approximately 1,000 IU.[6]

An observational study assessed the efficacy and safety of rFXIII in Italian patients with varying degrees of FXIII deficiency over nearly four years. It confirmed its effectiveness and emphasized the importance of initiating prophylaxis in cases of severe FXIII deficiency at birth or upon diagnosis.[3]

This article aims to report two cases of Hereditary FXIIID with different clinical features, highlighting the characteristics of the mild and severe forms and discussing the need for investigation of this pathology in patients with unusual hemorrhagic conditions.

CASE REPORT

Table 1: Therapeutic Management of FXIIID (ADP: adenosine diphosphate, ADR: adrenalin).

Procedure/Clinical Situation	Factor XIII Concentrate dose/range
Primary or Secondary Prophylaxis	10 IU/kg–20 IU/Kg at 4–6 week intervals
Acute bleeding episode	10 IU/kg–30 IU/Kg with monitoring (at least every 3–4 days) to assess dose range. Suspend when bleeding subsides
Intracranial Hemorrhage	20 IU/kg–30 IU/Kg. Monitor and maintain normal FXIII level until bleeding subsides
Surgery	20 IU/kg–30 IU/kg before the procedure and monitor to assess the dosing interval. Continue supplementation until healing.

Case 1

A 32-year-old male, the electrician, was referred to the hematology referral service for investigation of an atypical clotting disorder. Family history (sister) was positive for hemorrhagic diathesis; however, despite a thorough assessment by the healthcare service, no underlying coagulation disorders were identified in her. During the anamnesis, he denied being a descendant of consanguineous relationships. The patient reported post-trauma splenectomy at the age of 16 without bleeding and tooth extraction without complications.

In September 2020, he presented with an extensive spontaneous hematoma on the right thigh, which was reported after a minor bruise incurred from incidental contact with furniture. It was a trauma of a magnitude that would not typically warrant such a presentation in the absence of hemostatic disorders. During the episode, a cryoprecipitate transfusion was deemed necessary.

The patient's physical examination was normal. The results of the coagulation screening tests are described in Table 2.

Serology for Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) were performed with non-reactive results. There was a suspicion of FXIIID, which was confirmed after the measurement of FXIII (12.7% result), and the diagnosis of the mild form was defined.

Case 2

A 35-year-old female engineer was referred for hematological investigation due to a hemorrhagic condition (IH of undefined cause). In the clinical history, a report of unusual bleeding of the umbilical cord was identified, requiring transfusional support, hypermenorrhea, and the appearance of spontaneous hematomas. In December 2010, he had a traumatic brain injury in a mild automobile accident, which determined nystagmus, aphasia, motor incoordination, and headache with a diagnosis of IH (Figure 1) with hematoma formation in the cerebellar region.

The patient received a transfusion of platelet concentrate and fresh frozen plasma in the emergency room. Her family history was negative for hemostatic disorders. Physical examination at the hematological consultation revealed hematomas in the lower limbs, and the neurological evaluation was normal. The coagulation assessment is described in Table 2. Screening for Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) were negative. The FXIII dosage performed identified levels below 1%, with a diagnosis of the severe form of FXIIID, and a protocol of prophylactic infusion of FXIII was initiated.

DISCUSSION AND CONCLUSION

Duckert et al[11] made the first report involving FXIIID in 1960 and described a seven-year-old boy admitted to an emergency department due to ICH. The boy was born to consanguineous parents and had a history of bleeding from the umbilical stump (after 12 days of delivery), bruises, and disproportionate bleeding.[11] There is in the literature a time window of approximately eight years until the next publication and, until then, less than 100 case reports of congenital FXIIID were described in the MedLine database, via PubMed, evidencing the scarcity of literature involving this rare topic and the importance of registering new cases that can enrich the literature.

Cohen EL et al[12] describe the case of a male baby, born at term, vaginally delivered, and circumcised on the first day of life, who presented bleeding on the second and third subsequent days, with admission to the Intensive Care Unit (ICU) neonatal and diagnosed with severe congenital FXIIID.[12] A clinical manifestation similar to case 2 of the present study, with intercurrences already in the first days of life, due to the severe form of FXIIID, with an FXIII dosage of less than 1%.

Xu PP *et al (*2021), reported a case series involving 2 siblings – girl aged 4 years and 10 months and a boy aged 2 years and 8 months – children of non-consanguineous parents with a history of recurrent IH.[13] The siblings' laboratory tests including coagulation, liver, and kidney function tests with 24-hour insoluble Clot Solubility Test (CST) were normal. Genetic evaluation detected the homozygous variant c.2150A>G, p.H717R, of the F13A1 gene in both children. The clinical

Table 2: Laboratory test results – Case 1 and Case 2 (ADP: adenosine diphosphate. ADR: adrenalin).

Laboratory Tests	Case 1	Case 2	Reference Values
Activated Partial Thromboplastin Time (aPTT)	28″	34″	28″-38″
Prothrombin Activity (PA)	96%	100%	100%
Platelets Count, Platelet Aggregation Curve (ADP, Ristocetin, ADR, collagen)	Normal	Normal	Normal
Fibrinogen	450 mg/dl	280 mg/dl	175-450 mg/dl
FVIII coagulation assay	128.80%	100%	50-150%
FIX coagulation assay	115.80%	120%	50-130%
FXIII coagulation assay	12.70%	<1%	70-140%
Von Willebrand Factor and Ristocetin Cofactor	183%/98%	63%/112%	60-240%

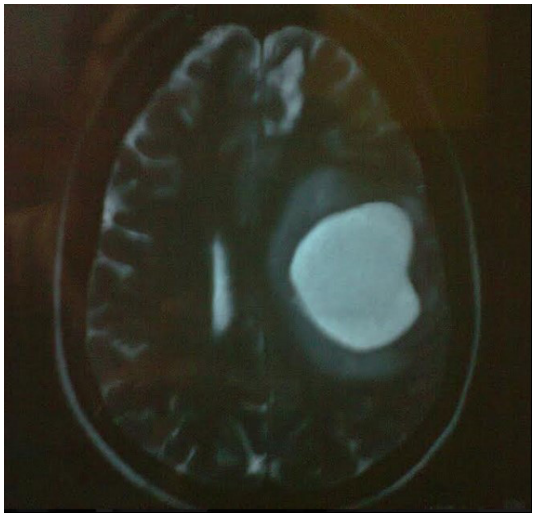

Figure 1: Brain Nuclear Magnetic Resonance from Case 2.
Subacute intraparenchymal hematoma measuring 5.5x4.5 cm located in the subcortical white substance, promoting mass effect with the erasure of the cortical grooves, partial collapse of the left lateral ventricle and deviation of the midline structures to right by 0.6 cm.

manifestations and genetic analyses of the children confirmed the diagnosis of FXIIID subunit A. The CST showed values within the normal range, evidencing the low sensitivity of the test for diagnostic confirmation.

Xu PP *et al*. also presented in their series the case of a 47-year-old man, with no previous history of abnormal bleeding with severe pelvic hematoma with impact on locomotion after insignificant trauma diagnosed by abdominal computed tomography. Laboratory analysis for hematoscopy, platelet count, platelet aggregation, antiphospholipid antibodies, and thromboelastogram were normal. The CST showed complete dissolution in 4 hours, which suggested the diagnosis of FXIIID.[10] Literature data demonstrate that FXIIID can generate spontaneous or disproportionate bleeding due to mild trauma, as described by Xu PP et al[13], due to instability of the fibrin network, as occurred in Case 2 presented, an adult with extensive spontaneous hematoma in the thigh.

Ejaz M et al[14] report the case of a 5-year-old girl who was admitted to the pediatric emergency department with fever and short-term seizures, with initial suspicion of meningitis, without a satisfactory response to empirical therapy. The investigations revealed spontaneous hemorrhage in the right occipital lobe on CT. There were no signs of bleeding such as petechiae, hematoma, epistaxis, or gingival bleeding. Bleeding and coagulation tests were considered normal, except for the level of FXIII in plasma, whose result revealed FXIII activity of 16%. The child was transfused with cryoprecipitate and treated conservatively for IH, remaining asymptomatic and with monthly cryoprecipitate transfusions.[14] The occurrence of IH in this age group, without other predisposing factors, as

described in siblings by Xu PP et al[13], corroborates the literature data on FXIIID, including the normality of other routine laboratory bleeding and coagulation tests, demarcating strong indications of coagulopathy.

In the context of Congenital FXIII Deficiency, disorders involving A subunit genes are more prevalent and tend to exhibit greater severity. Patients with heterozygous FXIII-A deficiency typically do not manifest spontaneous bleeding but are susceptible to significant blood loss in situations characterized by hemostatic stress, such as trauma, surgical procedures, or childbirth 2.

Several laboratory tests, with different methodologies, are available in cases of suspected FXIIID, such as the CST, quantitative tests, such as those involving photometric and fluorimetric and antigen assays (immunoassays and ELISA – Enzyme Linked Immuno Sorbent Assay), for laboratory diagnostic purposes.[2,8]

The CST is a qualitative test and a method widely used to screen this pathology, which consists of verifying the stability of the clot, in the urea or monochloroacetic acid solutions: at adequate levels of FXIII, the clot becomes insoluble, but if the factor is deficient, the fibrin network dissolves. The dissolution time is directly proportional to the concentration of FXIII in the plasma.[13]

The CST, despite being a low-cost and easy-to-implement test, has low sensitivity and non-standardized methodology, which can lead to an erroneous or late diagnosis in heterozygous patients with mild to moderate mutations.[13]

The International Society on Thrombosis and Haemostasis has released an algorithm outlining the diagnosis and categorization of FXIII deficiency. According to it, the quantitative functional determination of FXIII activity should be the primary screening assay. A decline in FXIII activity prompts further investigations to determine the specific type of deficiency. It is advisable to conduct immunoassays to determine the plasma concentrations of FXIII-A2B2 complex, A and B subunit antigens, and the concentration of FXIII-A2 antigen in platelet lysate. When necessary, supplementary tests, such as assessing fibrin cross-linking through sodium dodecyl sulfate–polyacrylamide gel electrophoresis, may be conducted. Ultimately, it is recommended to detect the molecular genetic defects underlying FXIII deficiency.[8] In most reported cases of congenital FXIII deficiencies, particularly FXIII-A deficiencies, an ELISA to measure the FXIII-A subunit is generally sufficient.[2,8]

Cai et al[15] reported a patient that bioinformatics and amino acid sequence homology analyses identified homozygosity for terminal Cys328 mutation in the A subunit gene through direct DNA sequencing.[15]

Prompt diagnosis of this condition is crucial for enhancing the prognosis, as individuals with FXIII deficiency are susceptible to life-threatening bleeding in vital areas, including the intracranial, thoracic, and abdominal cavities, and the retroperitoneum.[1-3] To corroborate this, a comprehensive prospective study on laboratory coagulation parameters in extremely premature neonates demonstrated that Reduced factor XIII subunit A showed a significant association with death.[16]

The World Federation of Hemophilia's 2020 Annual Global Survey of the Worldwide Distribution of Rare Bleeding Disorders, published in October 2021, listed 1,637 patients with FXIIID registered in 77 regions. The data were mainly from Europe, highlighting the need for greater efforts to establish accurate diagnoses and improve information systems worldwide [9]. In accordance with that, maintaining an updated registry of patients with coagulopathies is crucial to understand the prevalence of the disease, its clinical aspects, treatment, and epidemiological surveillance. In Brazil, the computerized system Hemovida Web – Coagulopathies was developed to systematize this information, contributing to the effective monitoring, and planning of the National Program for Hereditary Coagulopathies. Moreover, the use of this system allows obtaining information about the quantity of coagulation factors dispensed to these individuals. The adherence and appropriate use of this system by healthcare services are essential for the success of the program, providing valuable data for decision-making in the Unified Health System (SUS) and government control agencies.[17]

Nonetheless, it is acknowledged that the scarcity of this condition, combined with the limited awareness among healthcare professionals and technical challenges in both pre- and post-analytical phases, presents a substantial impediment to achieving an early diagnosis. Furthermore, there is a scarcity of large-scale studies addressing the mortality rate in congenital FXIII deficiency, and there is also a notable absence of long-term follow-up studies to evaluate treatment outcomes. This situation contributes to the underdiagnosis of the condition and underscores the necessity for a better understanding of the primary manifestations of FXIII deficiency 2,7,8.

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The authors declare the absence of any conflicts of interest.

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