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Case Report

Congenital factor X deficiency: a case of unexplained neonatal anemia presenting with intracranial hemorrhage and hemorrhagic meningitis in the first month of life in a resource-limited setting

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ABSTRACT

Factor X (FX) deficiency is an exceptionally rare inherited autosomal recessive coagulation factor disorder, posing significant challenges due to its rarity and lack of evidence-based management guidelines. It can manifest in a spectrum of hemorrhagic symptoms, including life-threatening intracranial hemorrhages. Here, we reported a case of congenital FX deficiency who presented with intracranial hemorrhage (ICH), complicated by hemorrhagic meningitis within the first month of life, following unexplained neonatal anemia. Early diagnosis and prompt intervention are crucial, especially in resource-limited settings, for managing this rare condition. This case underscores the difficulties encountered in managing rare conditions like FX deficiency and emphasizes the necessity for further research and collaboration to establish standardized management protocols. By adding to the limited literature on Factor X deficiency, this case report emphasizes considering FX deficiency in severe neonatal anemia and highlights the importance of personalized patient care in addressing rare diseases.

Keywords: Factor X, Coagulation profile, Intracranial hemorrhage, Unexplained neonatal anemia, Meningitis

INTRODUCTION

Factor X, also known as Stuart-Prower Factor (named after the first individual patients), is a vitamin K-dependent glycoprotein that is indispensable in the coagulation cascade.[1] FX deficiency comprises approximately 10% of all rare coagulopathies, with an estimated incidence of 1 per 1 million in the general population. It is more prevalent in populations practicing consanguinity.[2,3] In India, the World Federation of Hemophilia recorded 67 cases of FX deficiency in 2023.[4] It can present as severe, moderate, or mild, depending on the plasma FX activity level. Severe forms typically manifest in infancy or early childhood with symptoms such as umbilical stump bleeding, mucosal hemorrhages, or intracranial hemorrhage.[5] This report described a case of a young infant with a history of unexplained neonatal anemia, later developing intracranial hemorrhage, and ultimately diagnosed with severe FX deficiency and currently being effectively managed with prophylactic therapy using fresh frozen plasma (FFP).

CASE REPORT

A 1-month-old male infant, born to non-consanguineous parents, full term via emergency cesarean section due to fetal distress, presented to the emergency room with decreased feeding, fever, and respiratory distress for 2 days.

The baby had been hospitalized at birth for severe neonatal anemia (Hb-4.6 g/dl), requiring a packed red blood cell transfusion (PRBC). There was no significant antenatal hemorrhage and no family history of bleeding

disorders. Normal cranium and abdomen ultrasound, normal platelet counts, and no significant drop in hemoglobin after transfusion ruled out ongoing blood loss. Hemolytic work-up also came negative, and the baby was discharged on day 10 of life with ongoing evaluation for the anemia.

Table 1: The coagulation profiles of the case.

Tests	Patient value	References
PT	More than one minute	12.5 S
aPTT (activated partial thromboplastin time	More than one Minute	27.6 – 42.5 S
INR (International normalised ratio)	6.04	
Thrombin time	11	12.0.- 16.0 S

Table 2: Factor assay results.

Test	Patient value	References
Factor VIII (%)	154	50- 150
Factor V	Leiden mutation not detected	
Factor X (%)	< 1	50- 150
Fibrinogen (mg/dl)	319	150-450

On examination, the baby was lethargic, severely pale, and had respiratory distress requiring oxygen support. A bulging anterior fontanelle raised suspicion of intracranial hemorrhage (ICH). The patient was intubated and mechanically ventilated. Empirical antibiotics and supportive measures were initiated. He had an episode of focal seizure on the same day of admission, necessitating phenobarbitone administration.

Laboratory investigations showed severe anemia (Hb-3.7 g/dl) with leukocytosis (27,000 /cumm), normal platelet count (3,45,000 /cumm), and prolonged prothrombin time (PT) (>100 secs). Liver and kidney function tests were normal. Lumbar puncture was deferred due to suspected ICH with coagulopathy.

Treatment was initiated for sepsis with coagulopathy with suspected ICH. The baby received empirical antibiotics, PRBC and FFP transfusions, antiepileptic medication, and other supportive care.

Persistent bleeding at venipuncture sites and persistent prolonged prothrombin time despite vitamin K administration, with a history of unexplained severe neonatal anemia, prompted further coagulation testing. A common pathway factor assay confirmed severe factor X deficiency, with normal levels of factors II, VII, and VIII and normalization of PT/aPTT (activated partial thromboplastin time) with a mixing study with normal plasma. The coagulation profiles and factor assays are depicted in Tables 1 and 2, respectively. Next-generation sequencing was planned for genetic analysis but could not be done due to financial constraints.

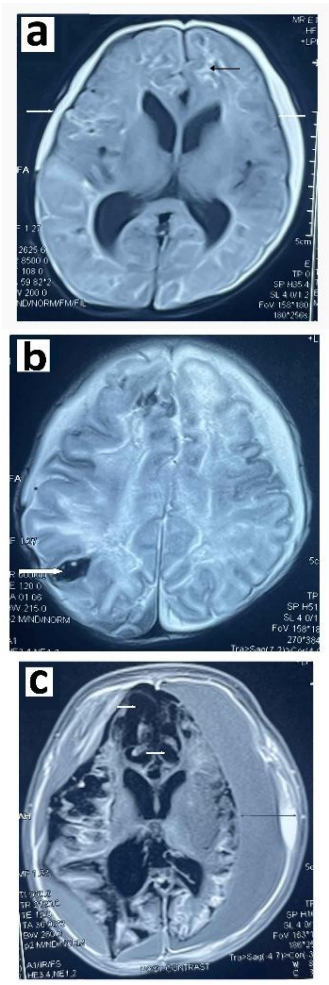

Figure 1: Axial MRI images showing (a) diffuse leptomeningeal enhancement (black arrow) and bilateral subdural fluid collection (white arrow); (b) hemorrhagic infarcts in the right parietal lobe; (c) acute to subacute subdural hemorrhage along the bilateral hemisphere (black arrow) and multicystic encephalomalacia (white arrow) in post-contrast T1 follow-up image.

To address the acute bleeding, the patient received 6 units of PRBC and 12 units of FFP. Prophylactic human prothrombin complex concentrate (PCC) was administered twice weekly, normalizing the coagulation profile and resolving the bleeding manifestations.

Subsequent MRI imaging of the brain, after stabilization, revealed hemorrhagic meningitis with bilateral subdural empyema and acute on chronic hemorrhage (Figure 1). Antibiotic therapy was thereafter escalated with a prolonged (6 weeks) duration. Due to the persistent subdural collection on further imaging, a burr hole procedure was performed by the neurosurgery team. Postoperatively, the patient remained hemodynamically

stable and was discharged on prophylactic FFP transfusion with close monitoring of neurological status.

Despite the challenges of managing the condition in a resource-limited setting, the infant remained stable with no further major bleeding episodes during follow-up over 12 months, but with neurological sequelae, including developmental delays.

DISCUSSION

Congenital FX deficiency poses diagnostic and therapeutic challenges due to its rarity and potential for severe bleeding complications. In resource-limited settings, the availability of coagulation assays and factor replacement therapies may be constrained.

This case illustrated the critical role of comprehensive evaluation in patients with intracranial hemorrhage with a history of severe neonatal anemia. Sepsis, a known cause of coagulopathy, potentially through disseminated intravascular coagulation, complicated the case. The bulging fontanelle and seizure were highly suggestive of ICH, which the coagulopathy could have exacerbated. The initial severe anemia, though previously treated, required further investigation to determine the underlying etiology. Coagulation profiles, which could have picked up the abnormality of coagulopathy, were not done as there were no signs of ongoing blood loss and sepsis in the previous admission.

The identification of severe congenital factor X deficiency explained the patient's prolonged bleeding and the hemorrhagic nature of the meningitis. The presentation of ICH, along with persistent bleeding from the venipuncture site, underscores the critical nature of Factor X deficiency and highlights the potential for life-threatening bleeding complications.

Depending on the functional activity of Factor X (FX: C), patients are classified as severe (FX: C, <1%), moderate (FX: C, 1-4%), and mild (FX: C, 6-10%). Severity of bleeding increases with decreasing FX-C activity.[6] In our case, we observed a severe FX deficiency (<1%) manifested with life-threatening ICH, consistent with sporadic cases reported in our country.[5,7,8]

The prolonged PT warranted prompt correction with FFP to mitigate the risk of further bleeding. The prompt initiation of broad-spectrum antibiotics and supportive care, including mechanical ventilation, was crucial for the patient's survival.

The concomitant presence of hemorrhagic meningitis and subdural empyema underscores the importance of a multidisciplinary approach involving pediatricians, hematologists, and neurosurgeons in optimizing patient care. Timely initiation of empirical antibiotics targeting potential pathogens implicated in central nervous system infections, coupled with correction of the coagulopathy with FFP and PCC and neurosurgical intervention to drain subdural collections, contributed to favourable outcomes in this case.

The standard therapeutic intervention for FX deficiency typically involves FFP transfusions. Alternative treatments include prothrombin complex concentrates (PCCs), dual-factor IX/X therapy, and human plasma-derived FX concentrate, with single-factor concentrates being the preferred modality when feasible.[9] Although the plasma derived FX concentrate (Coagudex), the first and only specific treatment for hereditary FX deficiency, is already approved and recommended over FFP and PCCs, high cost and lack of commercial availability limit its use in India.[3] In this case, the risk vs. benefit of FFP versus PCC was considered, as FFP has a higher risk of transfusion reaction.[9] However, cost-effectiveness of FFP over PCC in resource-limited settings was considered, and FFP was utilised for prophylaxis after discharge, reflecting the adaptation of treatment strategies with readily available resources.

Genetic testing would have been beneficial to confirm the diagnosis and provide genetic counselling, however, it was not performed due to financial constraints.

The neurological sequelae, including developmental delays, require ongoing monitoring and management.

CONCLUSION

This case highlights the importance of considering rare coagulation disorders such as factor X deficiency in infants presenting with unexplained neonatal anemia and neurological symptoms. Early diagnosis and targeted therapy can significantly improve outcomes for affected individuals, even in resource-constrained environments. This case report emphasizes the challenges in diagnosing and treating such rare conditions in resource-limited settings, with careful monitoring and adaptation of treatment strategies.

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