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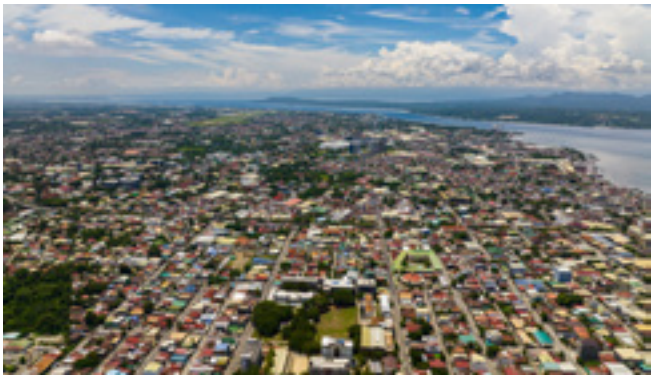
CASE STUDY

The first reported case of factor X deficiency in a Filipino child – case study

Kristian Dorell Masacupan, Allan Robert Racho, Maria Luz Del Rosario, Loralyn Mae Lagara-Aranas

Factor X (FX) deficiency is an extremely rare inherited bleeding disorder affecting one in 1,000,000 people. According to the most recent published census of the World Hemophilia Federation, to date there is no reported case of FX deficiency in the Philippines. Rare disorders like FX deficiency often go unrecognised or misdiagnosed. Here, we report the first case of FX deficiency in a Filipino child. A two-month-old male child with consanguinity was referred to our hospital due to bleeding episodes. On the third day of life, he had haematomas to the cervical area and upper extremities, and spontaneous bleeding of the umbilical cord was noted. Initial workup showed prolonged PT and aPTT. Factor deficiencies including FVIII and FIX were considered, however assays were normal. At six weeks of age, the child developed convulsions and deteriorating neurologic status. CT scan showed subarachnoid haemorrhage. The child was referred for further workup. Additional assay of clotting factors showed decreased FX activity at less than 1% and he was diagnosed with severe congenital FX deficiency. Following recurrent intracranial bleeding, the child has been observed to have permanent neurological deficit. This case highlights the importance of timely and accurate diagnosis to prevent life-threatening complications and the risk of permanent disability. Despite being an extremely rare disorder, the incidence of FX deficiency is estimated to be higher in populations where consanguineous marriages are common. Awareness of this rare condition must be emphasised. Families may benefit from screening through coagulation studies as well as genetic counselling, especially when planning future pregnancies. The rarity of this condition has not allowed for the establishment of evidence-based management guidelines, with treatment based on limited literature. Despite development of FX-specific clotting factor products, the high cost and limited availability impact their use in low-resource settings.



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This case report, which presents a diagnosis of severe FX deficiency in a two-month-old child, highlights the importance of timely and accurate diagnosis to prevent life-threatening complications and risk of permanent disability

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Factor X (FX) deficiency is an extremely rare inherited bleeding disorder [1]. It is an autosomal recessive disorder estimated to affect one in 1,000,000 people in the general population [2]. Characterised by a lack in the production of FX clotting factor, FX deficiency is classified as severe, moderate or mild disease depending on the functional assay level (severe <1%; moderate 1-4%; mild 6-10%) [1]. The amount of residual protein activity correlates with the severity of the disease. For effective haemostasis, a level of >10% FX is thought to be adequate [3]. The most frequent bleeding symptoms are mucocutaneous [4]. Symptoms include easy bruising, epistaxis, gum bleeding, menorrhagia, haematuria, haematomas, haemarthrosis, gastrointestinal (GI) bleeding, intracranial haemorrhage and umbilical cord bleeding. People with mild FX deficiency are usually asymptomatic and may be diagnosed only during routine screening, or because of positive family history. Moderately affected individuals may be recognised only after haemostatic challenge, such as surgery, trauma or menstruation. In the most severe form, symptoms are highly variable and usually begin at or shortly after birth [5].

As with other rare disorders, people with FX deficiency often go unrecognised or are misdiagnosed [5]. According to the most recent published census of the World Hemophilia Federation (WHF) [6], to date there has been no reported case of FX deficiency in the Philippines. Here, we present the first reported case of FX deficiency in a Filipino child.

CASE REPORT

A two-month-old male who presented with bleeding episodes during the neonatal period was referred to our institution. The patient is a child of Muslim parents, both of whom are 22 years old and apparently healthy. There is no history of bleeding tendencies in the family, however consanguinity was documented with the parents being second cousins. The child is the only living child of three pregnancies, the previous two pregnancies having resulted in spontaneous abortions during the first trimester.

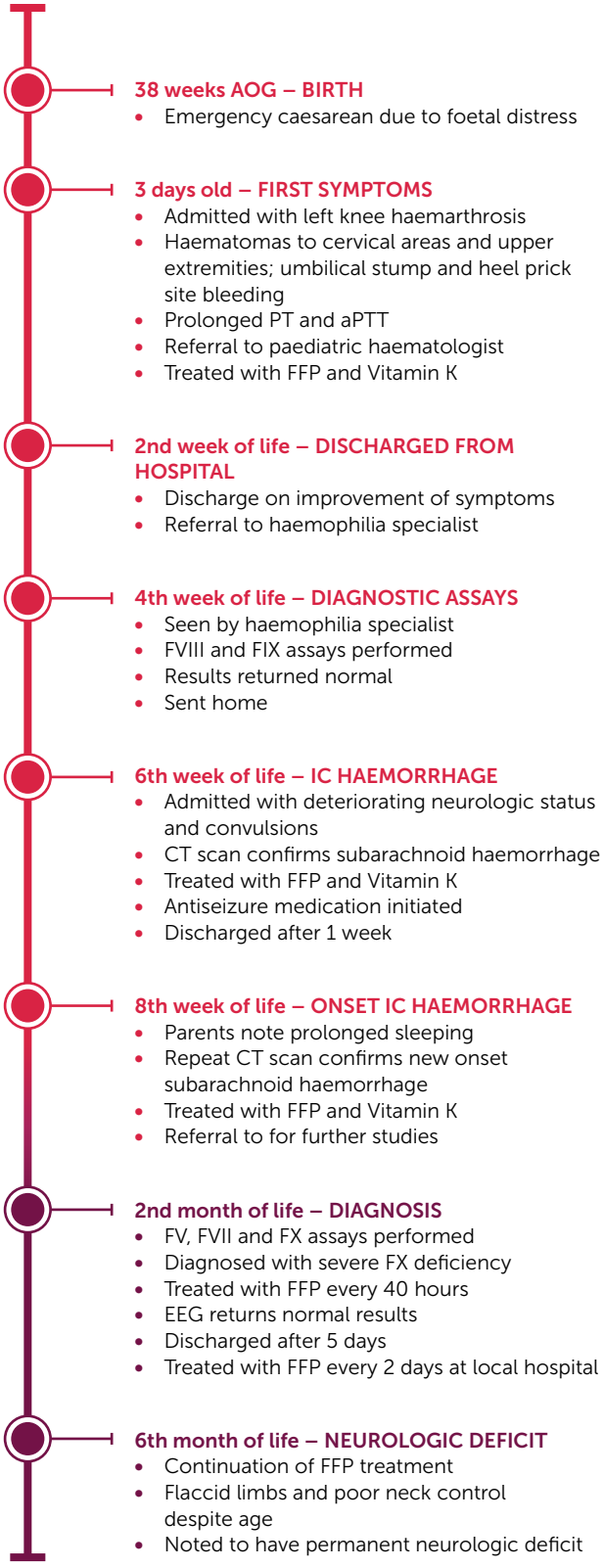
The child was born at 38 weeks' gestation via emergency caesarean section due to foetal distress, at a private hospital. On birth, the child was with good cry and was active, but on the third day of life he was noted to have a haematomas on the cervical area and upper extremities. Spontaneous bleeding was observed upon removal of the cord clamp and bleeding from the heel prick site for neonatal screening was also noted. Initial workup showed a markedly prolonged prothrombin time (PT) at 120 seconds with INR >6 and activated partial thromboplastin time (aPTT) of 160 seconds. The child was given a single dose of vitamin K 1.5mg IV and fresh frozen plasma (FFP) at 15ml/kg every 8 hours, and was referred to a paediatric haematologist. There was apparent control of bleeding and gradual resolution of the haematomas, and he was discharged on his second week of life. The paediatric haematologist suspected possible haemophilia A or B and referred the child to a haemophilia specialist in Davao City, where he was seen aged one month. An initial factor assay revealed normal factor VIII (FVIII) and factor IX (FIX) levels and the child was sent home apparently well.

During the sixth week of life, the child developed convulsions with deteriorating neurologic status. He was readmitted to his home hospital and a CT scan showed subarachnoid haemorrhage. FFP transfusions were again scheduled every 8 hours together with vitamin K administered every 12 hours. Antiseizure medications were also started. With improved neurologic status, the child was discharged after one week. However, at eight weeks old, his mother noted that he had prolonged sleeping time. A repeat CT scan at his home hospital showed a rebleed at the previous site of subarachnoid haemorrhage. The child was readmitted and was given FFP transfusions every 8 hours. When he was deemed stable to travel, he was referred to our institution in Manila for further diagnostic studies.

In Manila, further factor assays were performed immediately, specifically factors V (FV), VII (FVII) and X. Results showed normal activity for FV (111%) and FVII (64%), but decreased activity at less than 1% for FX. The child was diagnosed with severe congenital FX deficiency. He was transfused with FFP at 15ml per kilogram every 40 hours for three days. Other therapeutics were considered. These included a clotting factor product specific to FX deficiency, however the product was not available locally and would have required approval from the Philippines Food and Drug Administration (FDA).

On his second hospital day, the child was referred to a paediatric neurologist and an EEG was performed. The EEG results returned normal and the child's antiseizure medications were tapered off. On the fifth hospital day, he remained stable and was discharged home. Currently, the child attends a local hospital in his home city every two days to receive regular FFP transfusions with repeated intravenous cannulations. Despite this, he continues to experience recurrent intracranial bleeding (the severity and volume of the

Figure 1. Timeline showing patient history from birth to diagnosis, including current status



PT: Prothrombin time
aPTT: Activated partial thromboplastin time
FFP: Fresh frozen plasma
CT scan: Computerised tomography scan
IC haemorrhage: Intracranial haemorrhage

bleeds have not been relayed). Aged six months old, his paediatric haematologist observed that the child has a permanent neurologic deficit, with flaccid limbs and poor neck control. Figure 1 presents a timeline from the child's birth to six months of age, showing key episodes in the diagnostic journey.

The child's parents have been advised on coagulation screening and genetic counselling. Genetic screening has also been advised, however it is not available to the parents locally. Members of the care team have explained the inheritance pattern of FX deficiency to them and the possibility of other family members inheriting this rare disorder. The child's parents have agreed to be referred to an adult haematologist for coagulation studies but these are yet to be performed.

DISCUSSION

FX, or Stuart-Prower factor, is a vitamin K-dependent coagulation factor [7]. Synthesis occurs in the liver and, similar to other vitamin K-dependent proteins, requires post-translational modification to achieve maturation. The active form (FXa) is a catalytic serine protease which is the most important activator of prothrombin [8] and is positioned at the convergence of the extrinsic and intrinsic pathway. FX plays a crucial role as the first enzyme in the common pathway to cross-linked fibrin clot formation [9], placing it in a unique position in the coagulation cascade. Because of this, FX deficiency is suspected when both PT and aPTT are elevated, as in the case reported here.

In general, a diagnosis of FX deficiency is based on identification of characteristic symptoms, a detailed patient and family history, a thorough clinical evaluation, and specialised tests. FX deficiency can be investigated by functional activity assay, immunological assay, or chromogenic assay [1], and diagnosis can be confirmed by any of these. Molecular genetic testing can also confirm diagnosis but is usually not necessary [5]. FX assay is not readily available in the Philippines; assays for FV, FVII and FX are offered only at our institution in Manila. People with severe FX deficiency may present in the neonatal period with umbilical stump bleeding [10]. This symptom is reported in 28% of those diagnosed [11] and was observed in the case reported here. Intracranial haemorrhage in the neonatal period is reported in 26% of patients and is usually fatal [12]. Again, the child in our case suffered intracranial bleeding. Despite suspecting a factor deficiency from the start, the delay in diagnosis resulted in the child developing life-threatening complications and possible permanent neuro-disability.

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FX deficiency is inherited in an autosomal recessive pattern [5]. Disorders inherited in a recessive pattern occur when an individual inherits the same variant gene for the same trait from both parents. If only one gene for the disease is inherited, the person will be a carrier of a disease and will usually remain asymptomatic. In the case reported here, both parents may have been heterozygote carriers of the defective F10 gene, placing them at high risk of having an affected child.

The incidence of FX deficiency is shown to be higher in populations in which consanguineous marriage is common, for example in Middle Eastern populations [13]. Analysis of pedigrees in those diagnosed with FX deficiency often reveals consanguineous parents in these populations, and the prevalence of heterozygous FX deficiency (carrier state) may be as high 1:500 [14]. FX deficiency accounts for 1.3% of people with inherited coagulation deficiencies in Iran compared to the 0.4% and 0.5% Italy and UK, respectively. Family members of affected individuals may benefit from coagulation screening. Families should also be educated on the inheritance pattern of this disorder and the possibility that it may affect other family members. Genetic counselling is advised. In women with FX deficiency, pregnancy is high risk for adverse outcomes, including miscarriage, premature labour and haemorrhage [15].

Treatment for FX deficiency involves replacement therapy, usually through FFP or prothrombin complex concentrates (PCC) [11]. The biological half-life of infused FX is 20 to 40 hours [16]. A loading dose of 10 to 20 ml/kg of FFP, followed by 3-6ml/kg twice daily will usually achieve trough levels above 10%. PCC or highly purified FIX concentrates may contain therapeutic amounts of FX. PCC products with a FX: FIX ratio of 1:1 will increase plasma levels approximately 1.5% for every 1unit/kg body weight given. Because of the long half-life, daily treatment may result in increasing levels and is usually not required. However, care is warranted as frequent transfusion can result in allergic reactions. Frequent FFP transfusion is also associated with transfusion-associated lung injury, especially in neonates. The use of PCC has been associated with thrombosis due to the presence of activated coagulation factors; disseminated intravascular coagulation (DIC) and venous thromboembolism (VTE) have been documented. Development of inhibitory antibodies has not been established in patients treated with FFP or PCC [17].

In 2015, the United States (US), the FDA has approved Coagadex, plasma-derived FX concentrate and the first and only treatment specifically for hereditary FX deficiency [18]. A study of Coagadex prophylaxis in children under 12 with FX deficiency by Liesner et al., including four children aged 0-5, found it to be very effective in reducing or preventing bleeding episodes, while advising caution around dosing as pharmacokinetics may differ in very young children [19].

Coagadex is designated as an orphan drug in the US [20]. Although commercially available elsewhere, it is not commercially available in the Philippines and other Asian countries and local FDA approval is warranted for its use. Despite improvements in medical insurance, the proportion of medical costs paid for by of out-of-pocket medical costs in the Philippines is still high [21], and the cost per 250 IU/vial of Coagadex is estimated at PHP 70,000 (USD 1233.50). Although single-factor treatment is generally recommended for inherited bleeding disorders over treatments such as FFP and PCC [19], the lack of commercial availability and high cost make this an unattainable option for treatment for people with FX deficiency in the Philippines.

To date, the rarity of FX deficiency has not allowed for the establishment of evidence-based management guidelines [1]. Individuals affected by this disorder are treated on limited literature and the opinions of clinicians. However, FX deficiency is recognised as one of the most serious rare bleeding disorders and symptoms can be life-threatening, especially in neonates and children with severe disease [19]. The recent publication of recommendations for the diagnosis and management of FX deficiency is to be welcomed [17], but consensus on treatment guidelines is still needed.

CONCLUSION

This case, in which a two-month-old male child of consanguineous parents was diagnosed with severe congenital FX deficiency, highlights the importance of timely and accurate diagnosis to prevent life-threatening complications and the risk of permanent disability. Despite being an extremely rare disorder, the incidence of FX deficiency is higher in populations where consanguineous marriages are common and, where less rare bleeding disorders are ruled out, should be a diagnostic consideration. Awareness of this rare disorder must be emphasised. Family members of affected individuals may benefit from screening through coagulation studies and genetic counselling is advised, especially when planning for future pregnancies. When a diagnosis is confirmed, families must be educated on the inheritance pattern and the possibility of other family members inheriting this rare disorder. Individuals

with FX deficiency are treated based on limited literature and the opinions of clinicians, and despite the development of specific FX clotting factor products, high cost and limited availability impact their use.

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