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Subarachnoid Hemorrhage in Congenital Factor X Deficiency: A Case Study and Literature Review

Sepideh Mohammadi,[1] Zahra Torab,[2] Soheila Aghakhani,[3] Mina Ghalandari,[4,*] Reyhaneh Mohammadimanesh,[5,*] Vahid Asgary,[6] Samira Louni Aligoudarzi,[7] and Mohammad Reza Younesi[8]

[1]Central Medical Laboratory, Ayatollah Taleghani Hospital, Tehran, Iran
[2]Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Faculty of Biological Science, Islamic Azad University, North-Tehran Branch, Tehran, Iran
[4]Emergency Medicine Specialist, Department of Emergency Medicine, Ayatollah Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Department of Chemical Engineering, Biotechnology Faculty of Engineering, Payame Noor University, Tehran, Iran
[6]Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[7]Mehr General Laboratories, Tehran, Iran
[8]Department of Hematology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[*]*Corresponding authors*: Mina Ghalandari, Emergency Medicine Specialist, Department of Emergency Medicine, Ayatollah Taleghani Hospital, Shahid Beheshti University of Medical Sciences,Tehran, Iran. E-mail: Ghalandari mina@yahoo.com; Reyhan Mohammadimanesh, Department of Chemical Engineering, Biotechnology Faculty of Engineering, Payame Noor University, Tehran, Iran. E-mail: Reyhan.mohamadi@yahoo.com

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Abstract

Background: Inborn factor X deficiency (FXD) is a very rare (1: 500,000) hereditary coagulation disorder, which is characterized by clinical manifestations including hematoma, epistaxis, menorrhagia, ecchymosis, and central nervous system (CNS) or gastrointestinal (GI) bleeding (depending on the zygosity). In homozygote patients, the risk of spontaneous intracranial hemorrhage (ICH) is high.
Objectives: The aim of this investigation was to study and long-term follow-up of the patients with FXD and ICH. In addition, we investigated their frequent bleeding symptoms throughout their life and the results were compared with results of other studies.
Patients and Methods: This study investigated 2 cases with spontaneous intracranial hemorrhage in patients with severe congenital (factor X) FX deficiency including a 3-year-old boy and a 1-month-old female neonate. The world literature was explored through the PubMed Medline and Scopus using appropriate and pertinent key words.
Results: The Patients referred to the hematology department due to the neurological complications such as vomiting, unconsciousness, prolonged nasal bleeding for recent 12 hours. They had no familial history of spontaneous CNS bleeding. The blood coagulation test analysis indicated a prolonged activated partial thromboplastin time (APTT) and also revealed a prolonged prothrombin time (PT) and the low levels of coagulation factor X implicating severe congenital FX deficiency. They followed up by our hematologists to prevent intracranial hemorrhage.
Discussions: As one ICH patient whose PT and aPTT suggest a coagulation disorder secondary to vitamin K deficiency or coagulation factor deficiency, unresponsiveness to vitamin K therapy should be useful to take FX deficiency into consideration.

Keywords: Factor X Deficiency, Intracranial Hemorrhage

1. Background

Homeostasis is caused by the interaction between platelets, coagulation factors, and anticoagulant proteins in blood vessels (1). Coagulation factor X (Stuart Prower factor) is one of the vitamin K-dependent serine proteases of the coagulation cascade, which plays a pivotal role in the homeostasis phenomenon as the first enzyme in the common pathway of fibrin formation (1, 2). The FX gene is 22 kb long and is located at 13q34-ter, 2.8 kb downstream of the F7 gene. The coding sequence is homologous to other vitamin K-dependent proteins such as FVII, FIX, and Protein C, and is divided into eight exons, each encoding for a particular domain within the protein (3, 4). FX is a vitamin K-dependent liver-produced serine protease, which serves an important role in the normal coagulation mechanism. Following activation by FIXa and its cofactor or by FVIIa and tissue factor, FXa catalyses the conversion of prothrombin to thrombin (1). Factor X deficiency (FXD) is a hereditary coagulation disorder, which is characterized by clinical manifestations including hematoma, epistaxis, menorrhagia, ecchymosis, and central nervous system (CNS) or gastrointestinal bleeding (depending on the zygosity) (2, 3). It is believed that it can be inherited in a autosomal recessive manner and can be frequently seen with congenital anomalies that is estimated to occur in 1: 1 000 000 individuals up to 1:500 carriers. In addition, the prevalence of the homozygous form is one in 500/000 - 1 000/ 000 of the general population. According to the levels of patients' plasma FX, the clinical manifestations of FX deficiency are varying from severe (< 1%) to mild (6% - 10%) (4, 5). Patients with moderate-severe deficiency (factor X level below 1%) may have symptoms similar to those of hemophilia A and B, including haemarthrosis, intracranial hemorrhage, and gastrointestinal (GI) bleeding (5). In-

tracranial hemorrhage is considered as an important presentation of the disease and the precise cause of intracranial hemorrhage in patients with FX deficiency is not well known, also due to the infrequent rate of FX deficiency, information about CNS bleeding complications and management is limited and is mostly derived from case reports (6, 7). In homozygote patients, the risk of intracranial hemorrhage (ICH) is high (8).

2. Objectives

In this study, 2 cases who had (many years ago) intracranial hemorrhage due to severe congenital FX deficiency were studied. The patients' baseline factor X level was < 1% of the normal range. Since a long-term follow-up was possible, we reported their frequent bleeding symptoms throughout their life; in addition, literature was reviewed regarding the patients with FX deficiency and ICH.

3. Patients and Methods

Tabriz University of medical sciences ethics committee approval was obtained, and the written informed consent obtained from each patient's parents, and the study was carried out in accordance with the principals of the Declaration of Helsinki. Information of both patients was obtained from their medical files and from a structured questionnaire filled by a physician by interview of the patients' parents. The world literature was explored through PubMed, Medline and Scopus using appropriate and applicable key words.

4. Results

4.1. Patient's Analysis

The first case was a 3-year-old boy who was referred to the hematology department of a general hospital in April 2009, due to the epistaxis, pallor, vomiting, and epileptic seizure. There was no significant family history of any bleeding disorder and hereditary coagulation factor deficiencies, but the parents were consanguineously married. He was born at 36 weeks by vaginal delivery weighing 3290 g with normal Apgar scores at birth. Brain computed tomography (CT) scan demonstrated an intracranial hemorrhage in the right parietal lobe and sever intracerebral hemorrhage in the left parietotemporal lobe (Figure 1). The blood coagulation test analysis indicated a prolonged activated partial thromboplastin time (APTT) of 160 s and revealed a prothrombin time of 125 seconds. Other laboratory results were as follows: mean corpuscular volume (MCV): 90 fl; WBC count: $13 \times 10^3/mm^3$ (with 45% segmented neutrophils, 50% lymphocytes, 2% band forms and 3% monocytes); ESR: 18 mm/h; Hb: 5.5 g/dL; Hematocrit 21%; and (platelet) Plt count: $285 \times 10^3/mm^3$. The coagulation factor X level was 0.6% and C-reactive protein was negative. Considering that there was no FX concentrate, prior the surgery to drain the hematoma, treatment was performed by infusion of fresh-frozen plasma (FFP) to achieve 10 - 20 IU/dL of FX plasma level to prevent the occurrence of repeated ICH. 2 hours later, FX plasma level was 20 IU/dL. It was not possible to carry out the operation in details. The neurological and clinical status was slightly recovered a couple of minutes after the surgery, and within a week his complaints were disappeared completely and he discharged after a normal neurological examination. The follow-up brain CT scan revealed that ICH was recovered 5 weeks later.

The next case was a 1-month-old female neonate, the twice-born child of a consanguineous Iranian family, (in January 2010) who was referred with neurological complications including vomiting, unconsciousness, bulged anterior fontanel, and prolonged nasal bleeding for recent 12 hours and she had no history of drug ingestion or trauma indicating ICH. In addition, physical examinations were as follows: head circumference: 45 cm, bodyweight: 5600 g, height: 66 cm, blood pressure: 60/40 mmHg, and and pulse rate: 152 beats min^{-1}. Screening clotting tests revealed a prolonged APTT of 140 s (normal range: 26 - 39 s) and a normal prothrombin time (PT) of 117 s (normal range: 11 - 13 s), also abdominal ultrasonography was normal. Other laboratory results were as follows: mean corpuscular volume (MCV): 70 fl; WBC count: $10 \times 10^3/mm^3$ (with 43% segmented neutrophils, 52% lymphocytes, 1% band forms and 4% monocytes); ESR: 16 mm/h; Hb: 5.1 g/dL; Hematocrit 23%; and Plt count: $291 \times 10^3/mm^3$. The coagulation factor X level was 0.5% and C-reactive protein was negative. Urgent brain CT scan demonstrated no evidence of congenital malformation, but revealed a severe intracerebral hemorrhage in the right parietal region with no vascular injury. Following FFP and 5 mg vitamin K administration (IM) the patient recovered with prophylactic and conservative therapy, the prolonged PT and APTT were normal, and the patient discharged on the 21st hospitalization day. The follow-up brain CT scan 5 and 11 weeks later revealed that ICH was recovering and recovered, respectively.

5. Discussion

FX deficiency comprises 9% of all rare bleeding disorders (RBDs), worldwide. Most of patients are suffering from severe form of the disease and represent clinical manifestations such as post dental extraction bleeding, post

Table 1. Prevalence of Clinical Presentations in Patients Through Their Life[a]

	Case 1	Case 2
1. Deep soft tissue hematoma	26	33
2. Post dental extraction bleeding	12	2
3. Epistaxis	39	24
4. CNS bleeding	11	26
5. Others	12	15

[a]Data are shown as (%).

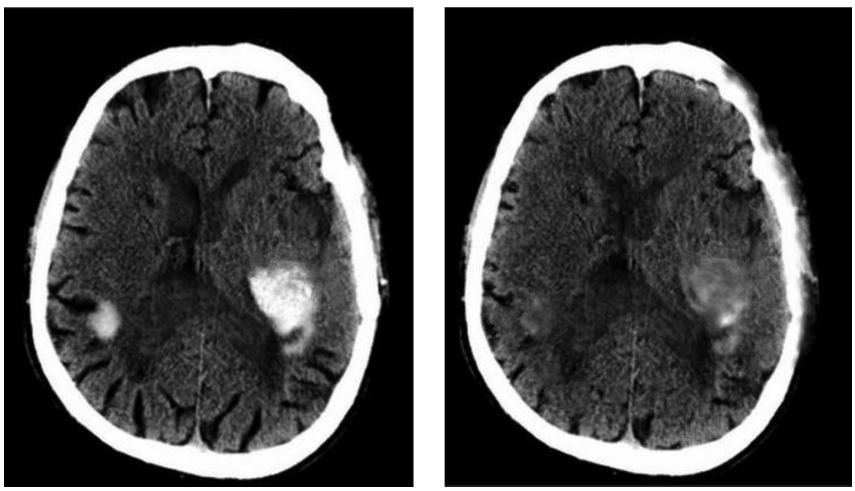

Figure 1. Case 1, Preoperative CT Image (Left) Representing Large Intracranial Hemorrhage in the Right Parietal Lobe and Sever Intracerebral Hemorrhage in the Left Parietotemporal Lobe, Postoperative CT Scan (Right) Demonstrating the Recovered ICH.

circumcision bleeding, and umbilical cord bleeding. Intracranial bleeding secondary to congenital FX deficiency is rare presentation of this condition in homozygote newborns (9). In the absence of a family history of bleeding disorders, most patients with FX deficiency are diagnosed after their first bleeding episode. In one of most comprehensive studies regarding rare bleeding disorders, Herrmann et al. (10) correlated the genotypes and bleeding phenotypes in 102 patients with FXD. Nine patients had ICH, and all but one had a homozygous genotype, the exception was compound heterozygous. The result of other studies is summarized in Table 2. FX deficiency was diagnosed in our patients by the bleeding manifestations, history of consanguinity and genetically malformation existence of their parents, prolongation of the PT and aPTT (with vitamin K deficiency consideration), and plasma FX levels under 1% of the normal range (11). Prophylactic therapy with FFP and prothrombin complex concentrates is currently considered as the most effective intervention to prevent bleeding episodes in patients with FX deficiency. In the medical centers of Iran, patients with severe FX deficiency are received regular prophylactic treatment regime of FFP to achieve 10 - 20 IU/dL of FX plasma level (12). Prothrombin complex concentrates contain the significant amounts of FX and have been used for the choice treatment of FX deficiency, but it should be used cautiously due to the increased risk of thrombosis. Prophylaxis against bleeding was successfully achieved in these patients by the additional administration of Prothrombin complex concentrates (8). In conclusion, patients with FX deficiency < 1 % are extremely rare and due to the limited data in the literature appears to be associated with recurrent spontaneous intracranial bleeding. As one ICH patient whose PT and aPTT suggest a coagulation disorder secondary to vitamin K deficiency or coagulation factor deficiency, responsiveness to vitamin K therapy should be useful to take FX deficiency into consideration.

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Table 2. Intracranial Hemorrhages Cases Due to Factor X Deficiency Reported in the Literature Including the Two New Studied Cases in This Article

Study	Number of Cases	Age at ICH/Sex	PT/PTT	Plt Count, mm^3	Management	Year
De Sousa et al. (13)	1	1 mon/F	180/166 sec	359/000	FFP/FIX concentrate	1988
Citak et al. (7)	1	3 mon / M	120/140 sec	447/000	FFP/vit K	2001
Peyvandi et al. (14)	1	2 days	> 120	u.k	FFP/vit K	2002
Ermis et al. (15)	2	2 mon/M	> 120 sec	304/000	FFP/vit K	2004
		18 days/F	115/175 sec	285/000	FFP/vit K	
Akhavan et al. (16)	1	u.k	> 120	Normal range	FFP	2007
Karimi et al. (17)	1	Neonate/M	u.k	normal	FFP	2008
Bereczyk et al. (18)	1	1 year/M	> 120	Normal range	u.k	2008
Herrmann et al. (10)	16	u.k	u.k	u.k	FFP/vit K	2008
Mota et al. (19)	1	Neonate/M	> 120	432/000	FFP	2010
Rauch et al. (20)	1	2 weeks/M	170/140 sec	u.k	FFP	2011
Present study	2	3 years/M	125/160	285/000	FFP	2016
		1 mon/F	117/140	291/000	FFP/vit K	

Abbreviations: u.k, Data unknown; M, male; F, female; mon, month; Plt, platelet.

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Footnote

Authors' Contribution: Sepideh Mohammadi and Vahid Askary participated in conceiving the study and laboratory examinations. Younesi Mohammad Reza participated in manuscript writing and edition. Samira louni Aligoudarzi helped to edit the manuscript, Sohila Aghakhani participated in the design of the study. Mina ghalandari performed statistical analysis and helped to collect data. Zahra Torab and Reyhaneh Mohammadi Manesh conceived the study, participated in its design supervision throughout the study. All authors read and approved the final manuscript. All authors report no conflicts of interest.

References

1. Doronin K, Flatt JW, Di Paolo NC, Khare R, Kalyuzhniy O, Acchione M, et al. Coagulation factor X activates innate immunity to human species C adenovirus. *Science.* 2012;**338**(6108):795–8. doi: 10.1126/science.1226625. [PubMed: 23019612].
2. Peyvandi F, Palla R, Menegatti M, Mannucci PM. Introduction. Rare bleeding disorders: general aspects of clinical features, diagnosis, and management. *Seminars In Thrombosis And Hemostasis.* 2009;**35**(4):349–55. doi: 10.1055/s-0029-1225757.
3. Menegatti M, Peyvandi F. Factor X deficiency. *Semin Thromb Hemost.* 2009;**35**(4):407–15. doi: 10.1055/s-0029-1225763. [PubMed: 19598069].
4. Beksac MS, Atak Z, Ozlu T. Severe factor X deficiency in a twin pregnancy. *Arch Gynecol Obstet.* 2010;**281**(1):151–2. doi: 10.1007/s00404-009-1090-4. [PubMed: 19396611].
5. Brown DL, Kouides PA. Diagnosis and treatment of inherited factor X deficiency. *Haemophilia.* 2008;**14**(6):1176–82. doi: 10.1111/j.1365-2516.2008.01856.x. [PubMed: 19141158].
6. de Sousa C, Clark T, Bradshaw A. Antenatally diagnosed subdural haemorrhage in congenital factor X deficiency. *Arch Dis Childhood.* 1988;**63**:1168–70.
7. Citak A, Ucsel R, Karabocuoglu M, Unuvar A, Uzel N. A rare cause of intracranial hemorrhage: factor X deficiency. *Pediatr Emerg Care.* 2001;**17**(5):349–50. doi: 10.1097/00006565-200110000-00007. [PubMed: 11673712].
8. Bolton-Maggs PH, Perry DJ, Chalmers EA, Parapia LA, Wilde JT, Williams MD, et al. The rare coagulation disorders–review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. *Haemophilia.* 2004;**10**(5):593–628. doi: 10.1111/j.1365-2516.2004.00944.x. [PubMed: 15357789].
9. Uprichard J, Perry DJ. Factor X deficiency. *Blood Rev.* 2002;**16**(2):97–110. doi: 10.1054/blre.2002.0191. [PubMed: 12127953].
10. Herrmann FH, Auerswald G, Ruiz-Saez A, Navarrete M, Pollmann H, Lopaciuk S, et al. Factor X deficiency: clinical manifestation of 102 subjects from Europe and Latin America with mutations in the factor 10 gene. *Haemophilia.* 2006;**12**(5):479–89. doi: 10.1111/j.1365-2516.2006.01303.x. [PubMed: 16919077].
11. Mansouritorghabeh H, Manavifar L, Banihashem A, Modaresi A, Shirdel A, Shahroudian M. An investigation of the spectrum of common and rare inherited coagulation disorders in North-Eastern Iran. *Blood Transfusion Trasfusione Del Sangue.* 2012:1–10.
12. Naderi M, Eshghi P, Saneei Moghaddam E, Alizadeh S, Dorgalaleh A, Younesi MR. Safety of human blood products in rare bleeding disorders in southeast of Iran. *Haemophilia.* 2013;**19**(2):90–2.
13. De Sousa C, Clark T, Bradshaw A. Antenatally diagnosed subdural haemorrhage in congenital factor X deficiency. *Archi Dis Childhood.* 1988;**63**:1168–70.
14. Peyvandi F, Menegatti M, Santagostino E, Akhavan S, Uprichard J, Perry DJ, et al. Gene mutations and three-dimensional structural analysis in 13 families with severe factor X deficiency. *Br J Haematol.* 2002;**117**(3):685–92. doi: 10.1046/j.1365-2141.2002.03486.x. [PubMed: 12028042].
15. Ermis B, Ors R, Tastekin A, Orhan F. Severe congenital factor X deficiency with intracranial bleeding in two siblings. *Brain Develop.* 2004;**26**(2):137–8. doi: 10.1016/S0387-7604(03)00119-0.
16. Akhavan S, Chafa O, Obame FN, Torchet MF, Reghis A, Fischer AM, et al. Recurrence of a Phe31Ser mutation in the Gla domain of blood coagulation factor X, in unrelated Algerian families: a founder effect?. *Eur J Haematol.* 2007;**78**(5):405–9. doi: 10.1111/j.1600-0609.2007.00836.x. [PubMed: 17391309].

17. Karimi M, Menegatti M, Afrasiabi A, Sarikhani S, Peyvandi F. Phenotype and genotype report on homozygous and heterozygous patients with congenital factor X deficiency. *Haematologica.* 2008;**93**(6):934–8. doi: 10.3324/haematol.12211. [PubMed: 18403394].
18. Bereczky Z, Bardos H, Komaromi I, Kiss C, Haramura G, Ajzner E, et al. Factor XDebrecen: Gly204Arg mutation in factor X causes the synthesis of a non-secretable protein and severe factor X deficiency. *Haematologica.* 2008;**93**(2):299–302. doi: 10.3324/haematol.11746. [PubMed: 18245654].
19. Mota L, Shetty S, Idicula-Thomas S, Ghosh K. Molecular basis of factor X deficiency cases from India. *Haemophilia.* 2010;**16**(4):693–7. doi: 10.1111/j.1365-2516.2010.02213.x.
20. Rauch R, Girisch M, Wiegand G, Schroeder W, Hofbeck M, Welisch E, et al. Factor X deficiency and intracranial bleeding: who is at risk?. *Haemophilia.* 2011;**17**(5):759–63. doi: 10.1111/j.1365-2516.2011.02591.x. [PubMed: 21682820].