

Congenital Factor VII Deficiency in Association With Bicuspid Aortic Valve and Multicystic Dysplastic Kidney Disease in a Child

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Abstract

Congenital factor VII deficiency is a rare bleeding disorder, with an incidence of 1:500,000. This case report describes an exceptionally unusual combination of congenital factor VII deficiency, multicystic dysplastic kidney disease and bicuspid aortic valve disease, in the same patient.

Keywords: Factor VII deficiency; Multicystic kidney dysplastic disease; Bicuspid aortic valve disease; Coagulopathy; Congenital

Introduction

Factor VII is a clotting factor that is part of the extrinsic coagulation cascade, which is a vitamin K-dependent factor [1]. Deficiency in this protein results in isolated prolongation of prothrombin time with normal activated partial prothrombin time [2, 3], and correction of this prolongation by 50/50 mixing study with normal plasma can aid the diagnosis by excluding presence of inhibitors [4]. Factor VII deficiency can be either acquired or congenital. The latter is a rare autosomal recessive disorder, reported as 1 in 500,000 [5]. Presentation of this disorder may vary from mild bleeding as in bruising and epistaxis, to severe life-threatening bleeding such as intracranial hemorrhage [3, 4]. In this study, we present a case of factor

VII deficiency associated with multicystic dysplastic kidney disease and bicuspid aortic valve disease (BAVD). There has been no direct genetic association between them and such co-existence has not been reported in the literature before.

Case Report

This is a case of a full-term baby boy, product of an emergency cesarean section due to fetal distress with birth weight of 3,720 g, Apgar score of 7 at 1 min and 9 at 5 min, with no resuscitation being required. The baby was admitted to neonatal intensive care unit (NICU) for 19 days for suspected sepsis, diagnosed at that time with G6PD and congenital factor VII deficiency by picture of bruises all over his body with qualitative G6PD screening test activity positive (deficient), prolonged prothrombin time (PT) of 37.5 s, high international normalized ratio (INR) of 3.9, normal activated prothrombin time (aPTT) of 35.1 s, confirmed by low factor VII level of 0.07; further results are shown in Table 1. Patient was started on regular recombinant activated factor VII. In addition, renal ultrasound was done and showed right multicystic dysplastic kidney disease, later on confirmed by DMSA scan. Patient was discharged from NICU after 19 days. Following this admission, he presented multiple times with bleeding complications in form of rectal bleeding and intracranial hemorrhage (ICH), and subsequently developed post ICH seizure disorder. At 5 months of age, echo was done as follow-up for aortic stenosis that was diagnosed at birth, which showed BAVD with pressure gradient 35 mm Hg, and patent foramen ovale with left to right shunt. There was positive history of consanguinity; mother and father are first-degree cousins. There is also positive family history of congenital factor VII deficiency in patient's first-degree cousin. Patient has two siblings, one with G6PD deficiency, while the other is healthy.

Discussion

BAVD is an inherited condition that results in a malformed, two-leaflet aortic valve, instead of the normal three-leaflet valve.

Cause of this malformation is not completely clear, but recent studies suggest an autosomal dominant component

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Table 1. Laboratory Results of Our Case

Test	Result	Reference
Hemoglobin (Hb)	15.8 g/dL	12.5 - 20.5
Prothrombin time (PT)	37.5 s	10.3 - 14
Activated prothrombin time (aPTT)	35.1 s	29 - 40
International normalized ratio (INR)	3.9	0.9 - 1.15
Factor VII level	0.07	0.7 - 1.2
D-dimer	0.4 mg/L FEU	0.17 - 0.64
Fibrinogen	413.9 mg/dL	160 - 350

FEU: fibrinogen equivalent units.

[6]. Another congenital anomaly in our case was multicystic dysplastic kidney disease, which is a congenital maldevelopment, characterized by a non-functioning kidney that contains multiple, varying in size, non-communicating cysts, separated by dysplastic renal parenchyma, and the absence of a normal pelvicaliceal system. It is usually a sporadic disease; however, few familial cases have been reported [7]. Congenital factor VII deficiency is an autosomal recessive disease, which is caused by a genetic mutation in factor VII gene, located on chromosome 13q34 [4, 8]. The unusual combination of the three congenital conditions with their different modes of inheritance makes it even rarer.

Countries with high numbers of consanguineous marriages like Saudi Arabia are at higher risk of congenital factor VII deficiency. During our literature review, there were very few studies on congenital factor VII deficiency in Saudi Arabia. As far as we know, there was only one published case report of a rare association with factor VII deficiency in form

of Hirschsprung disease in a new born female with extensive bleeding following an emergency laparotomy due to perforation. Blood work was done and congenital factor VII deficiency was confirmed [9]. A retrospective study conducted in Riyadh, Saudi Arabia, over 8 years, on 168 patients with hereditary bleeding disorder, showed only one patient with factor VII deficiency [10]. Another similar study established in the eastern province on 34 patients showed also one patient with congenital factor VII deficiency [11].

Congenital factor VII deficiency combined with other coagulation factor deficiencies has been stated in the literature. In a critical review of congenital combined deficiency of factor VII, and other factors including V, VIII, IX, X, XII and XIII, no clear genetic association was shown except for the combination of congenital factor VII and X deficiencies. It suggested that, the genes of both factors are very close and located on the long arm of chromosome 13q34; therefore large deletions may result in combined deficiency of both [12, 13]. Another suggested association with 13q deletions was cardiac anomalies, as in our case. A Chinese study proposed that 13q33.1-34 deletions might be related to cardiac development [14]. In the contrary, combined protein C deficiency and congenital factor VII deficiency has been described in a single study [15], the gene for protein C is encoded in chromosome 2, hence the combination of both is random. A number of studies listed in Table 2 [9, 13, 15-29] have shown unique combinations of factor VII deficiency and different associations with no evident explanation.

Conclusion

We present a case of three relatively uncommon disorders, congenital factor VII deficiency, multicystic dysplastic kidney

Table 2. Rare Associations With Congenital Factor VII Deficiency in the Literature

Age/study	Gender	Association
Two years [9]	Female	Hirschsprung disease
Seven years [13]	Male	Factor X deficiency
Twenty-one years [15]	Female	Protein C deficiency and pulmonary artery stenosis
Infant [16]	Male	Pulmonary atresia and hypoplastic right ventricle
Five weeks [17]	Unknown	Langdon down syndrome, complete endocardial cushion defect, and tetralogy of Fallot
Seventy-eight years [18]	Female	Severe aortic stenosis
Three years [19]	Unknown	Cleft palate
Thirty-two years [20]	Female	Autoimmune hepatitis type II and Grave’s disease
Twenty days [21]	Male	Chairi malformation
Seven and twelve years (siblings) [22]	Unknown	Hereditary spastic paraplegia
Twenty-five years [23]	Female	Jaw deformity
Forty-eight years [24]	Female	Neuroendocrine ampullary tumor
Unknown [25]	Unknown	Kidney stone
Two months [26]	Female	Anterior segment dysgenesis
Forty-one years [27]	Female	Multiple cerebral aneurysms
Two months [28]	Male	Inguinal hernia
Nine years [29]	Male	Partial monosomy of 13q and trisomy of 16p

disease and BAVD. It could be a rare association or syndrome, and further cases need to be reported.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained.

Author Contributions

Housam Almadani conceived of the presented idea, developed the theory and performed the computations and supervised the findings of this work. Alsaied, Alzahrani, Albogami, Asiri and Almelibari investigated lab and radiology. All authors discussed the results. Almadani wrote the manuscript and supervised the project. Alsaied and Almelibari contributed to the interpretation of the results. Almadani took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript. All authors analyzed the data. Almadani conceived the study. All authors discussed the results and commented on the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

- Lee CA, Berntorp EE, Hoots WK. Textbook of Hemophilia, 2nd ed. John Wiley & Sons; 2010.
- Lichtman M, Kaushansky K, Burns L, et al. Williams Manual of Hematology. 8th ed.; 2010.
- Mariani G, Bernardi F. Factor VII Deficiency. *Semin Thromb Hemost.* 2009;35(4):400-406.
- Ingerslev J, Kristensen HL. Clinical picture and treatment strategies in factor VII deficiency. *Haemophilia.* 1998;4(4):689-696.
- Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. *Blood.* 2004;104(5):1243-1252.
- Zipes D, Libby P, Bonow R, Mann D, Tomaselli G, Braunwald E. Braunwald's heart disease. 9th ed.; 2011.
- Belk RA, Thomas DF, Mueller RF, Godbole P, Markham AF, Weston MJ. A family study and the natural history of prenatally detected unilateral multicystic dysplastic kidney. *J Urol.* 2002;167(2 Pt 1):666-669.
- Cooper DN, Millar DS, Wacey A, Banner DW, Tud-denham EG. Inherited factor VII deficiency: molecular genetics and pathophysiology. *Thromb Haemost.* 1997;78(1):151-160.
- Zaher G, Jarullah J, Adam S, Kurdi M, Jamal M, Daman-houri G. Congenital factor VII deficiency in Hirschsprung disease patient, a novel case report. *J Pediatr Surg Case Rep.* 2016;15:28-30.
- Al-Fawaz IM, Gader AM, Bahakim HM, Al-Mohareb F, Al-Momen AK, Harakati MS. Hereditary bleeding disorders in Riyadh, Saudi Arabia. *Ann Saudi Med.* 1996;16(3):257-261.
- Ahmed MA, Al-Sohaibani MO, Al-Mohaya SA, Sumer T, Al-Sheikh EH, Knox-Macaulay H. Inherited bleeding disorders in the Eastern Province of Saudi Arabia. *Acta Haematol.* 1988;79(4):202-206.
- Girolami A, Ruzzon E, Tezza F, Allemand E, Vettore S. Congenital combined defects of factor VII: a critical review. *Acta Haematol.* 2007;117(1):51-56.
- Narang GS, Arora S, Pahwa JS. Combined Factor VII and X Deficiency. *Online J Health Allied Scs.* 2010;9(4):17.
- Huang C, Yang YF, Yin N, Chen JL, Wang J, Zhang H, Tan ZP. Congenital heart defect and mental retardation in a patient with a 13q33.1-34 deletion. *Gene.* 2012;498(2):308-310.
- Takeuchi Y, Saito Y, Ikenouchi H, Sugimoto T, Sugoh T, Sakata Y, Matsuda M, et al. Combined factor VII and protein C deficiency found in a patient with peripheral pulmonary artery stenosis accompanied by progressive pulmonary hypertension and hemoptysis. *Thromb Res.* 1988;51(2):117-126.
- Tokunaga C, Hiramatsu Y, Horigome H, Takahashi-Igari M, Noma M, Sakakibara Y. Palliative open heart surgery in an infant with factor VII deficiency. *Ann Thorac Surg.* 2003;76(6):2093-2094.
- Militaru M, Maris A. 515 A rare case of langdon down syndrome with complete endocardial cushion defect, tetralogy of fallot, deficiency of factor vii. *Arch Dis Child.* 2012;97(Suppl 2):A150-A150.
- Lux M, Kokofer A, Schreiber C, Torgersen C. Surgical Aortic Valve Replacement in an Adult Patient With Congenital Factor VII Deficiency: A Case Report of Perioperative Coagulation Management. *J Cardiothorac Vasc Anesth.* 2015;29(6):1636-1638.
- Pirrello R, Siragusa S, Giambona C, D'Arpa S, Cordova A, Moschella F. Bleeding prophylaxis in a child with cleft palate and factor VII deficiency: a case report. *Cleft Palate Craniofac J.* 2006;43(1):108-111.
- Gerova V, Tankova L, Nakov V, Taneva G, Nakov R. Simultaneously diagnosed autoimmune hepatitis type II, Grave's disease and congenital factor VII deficiency. *Am J Med Case Rep.* 2015;3(9):269-271.
- Bay A, Aktekin E, Erkutlu I. A rare combination: con-

- genital factor VII deficiency with Chiari malformation. *Blood Coagul Fibrinolysis*. 2015;26(8):946-948.
22. De la Corte-Rodriguez H, Rodriguez-Merchan EC, Alvarez-Roman MT, Hernandez-Moreno AL. Coexistence of Factor VII Deficiency and Hereditary Spastic Paraplegia in Two Siblings. *Case Rep Hematol*. 2016;2016:1351873.
 23. Rokutanda S, Yoshida M. A case of sagittal splitting ramus osteotomy and genioplasty in a patient with congenital factor VII deficiency. *Acta Medica Nagasakiensia*. 2015.
 24. Natarajan R. Local resection of ampullary neuroendocrine tumor with high risk factor (Factor VII Deficiency) - case report. *University Journal of Surgery and Surgical Specialities*. 2016.
 25. Okan V, Yilmaz M, Seckiner I, Erturhan S, Ciftci S, Pehlivan M. Kidney stone surgery in a patient with factor VII deficiency: case report. *Journal of Reconstructive Urology*. 2010.
 26. Beby F, Meunier S, Cochat P, Roche O, Aptel F, Burillon C, Denis P. Anterior segment dysgenesis in a child with factor VII deficiency. *Clin Ophthalmol*. 2007;1(3):335-337.
 27. Schilling AM, Heidenreich JO, Oldenburg AC, Pietila T, Stendel R, Wolf KJ. Multiple cerebral aneurysms in factor VII deficiency. *AJNR Am J Neuroradiol*. 2004;25(5):784-786.
 28. Bhosale M, Salvi S, Kulkarni R, Rangarajan S. Management of an infant with congenital factor VII deficiency presenting with obstructed inguinal hernia. *J Clin Neonatol*. 2018;7(2):108.
 29. Brooks BP, Meck JM, Haddad BR, Bendavid C, Blain D, Toretsky JA. Factor VII deficiency and developmental abnormalities in a patient with partial monosomy of 13q and trisomy of 16p: case report and review of the literature. *BMC Med Genet*. 2006;7:2.