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ABSTRACT

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EDITORIAL

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Combined deficiency of vitamin K-dependent coagulation factors and extensive hemorrhage

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Factor (F) II, FVII, FIX, and FX are known as vitamin K-dependent coagulation factors, as γ -carboxylation of the glutamine (Glu) residues is a critical step for their coagulant activities [1–3]. Gamma-carboxylation of the Glu residues which is mediated by γ -glutamyl carboxylase (GGCX) and reduced vitamin K (KH₂) as its cofactor, is necessary for binding of calcium ions which then allows binding to phospholipid membranes. Another enzyme playing an important role in this cycle is called vitamin K epoxide reductase (VKOR). The VKOR catalyzes reconversion of vitamin K epoxide (KO), which is produced during the last reaction, to KH₂ [2, 4]. Some natural anticoagulants including protein C, protein S, and protein Z also requires Glu residues to be modified into γ -carboxyglutamate (Gla) residues and therefore there are low levels of protein C and protein S in the deficiencies of GGCX or VKOR. The deficiency of vitamin K-dependent coagulation factors can be an inherited or acquired disorder. In inherited form of disease, the disorder is usually manifest in infancy period, although it may also remain latent for a short time. Clinical manifestations are depending on the level of reduced coagulation factors [2, 5–7]. Acquired vitamin K-dependent coagulation factors are more common than congenital deficiency of

these factors and only a few congenital form of disorders were reported up to now. Acquired deficiency can results in different conditions including liver disease and malabsorption [8, 9]. In the present study, we reported a woman with acquired vitamin K-dependent coagulation factors with extensive menorrhagia. We described a 43-year-old female with simultaneous decrease in vitamin K-dependent coagulation factors. She was born from an Iranian mother and a Russian father. Three years later, patient was referred with extensive menorrhagia and was hospitalized for management of her severe bleeding as well as diagnosis of disorder. In routine coagulation tests, prothrombin time (PT, normal range: 11.7–14.2 s) and activated partial thromboplastin time (APTT, normal range: 29–40 s) that was performed by STA compact automated coagulometer (Stago, Paris, France) both were prolonged while bleeding time (BT) (Ivy method) and platelet count (Sysmex kx21 hematology analyzer) were normal. In the mixing study, PT and APTT were corrected that indicating factor deficiency rather than inhibitor formation against deficient coagulation factors. Factor activity for all coagulation factors were performed (STA, compact automatic coagulometer, Diagnostica, Stago) except on factor XIII (FXIII) that was screened by clot solubility test as described by Dorgalaleh et al. [7]. Vitamin K-dependent coagulation factors level were abnormal (Table 1).

Subsequently, patient's liver statues was evaluated by liver sonography (Mountain View, CA, USA) and liver function tests (LFTs) and cholesterol and triglyceride also were (auto analyzer, Hitachi 7250 special; Hitachi, Tokyo, Japan) but any abnormality was not observed except in a marked hypertriglyceridemia. The patient does not suffer from gastrointestinal disorder. The patient does not experience warfarin therapy in her life. Since patient suffered from severe bleeding, high dose (15 mg daily) of oral and parenteral vitamin K was administrated and vitamin K-dependent coagulation factors were rechecked but any changed was not observed and patient's bleeding was not stopped. Subsequently, the patient was received prothrombin complex concentrates (PCCs) that stopped patient's bleeding.

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Table 1: Results of coagulation and biochemistry tests of patient and her father

Test	Patient	Father	Normal range
Prothrombin time (sec)	70	13	11.7–14.2
APTT (sec)	>120	38	29–40
BT (IVY) (Min)	3	-	2–7
Fibrinogen (mg/dL)	300	-	200–400
Factor II (%)	3	85	70–120
Factor V (%)	120	-	70–120
Factor VII (%)	8	83	55–170
Factor VIII (%)	180	-	60–150
Factor IX (%)	11	-	60–150
Factor X (%)	1	85	70–120
Factor XI (%)	100	-	50–110
Factor XII (%)	100	-	50–120
Protein C (%)	43	-	70–130
Protein S (%)	35	-	50–123
ALT (IU/L)	11	-	5–40
AST (IU/L)	9	-	5–40
ALP (IU/L)	230	-	64–306
Triglyceridemia (mg/dL)	1200	-	150–199
Cholesterol (mg/dL)	420	-	<200
Bill-T (mg/dL)	0.5	-	Up to 1.4
Bill-D (mg/dL)	0.1	-	Up to 0.5

APTT: Activated partial thromboplastin time, BT: Bleeding time, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase

Due to economic sanctions, PCC limitedly was available in Iran and FEIBA (Factor Eight Inhibitor Bypassing Activity, Vapor Heated; Baxter, Vienna, Austria) was administrated in a dose of 50 U/kg as an alternative. Although, therapeutic response was not similar to PCC but severity of bleeding was reduced. The patient had six sons and three brothers without any history of abnormal bleeding.

Although patient's bleeding was managed by PCC and FEIBA but she was hospitalized due to extensive hemorrhage several times and PCC and FEIBA again were used for management of bleeding. At last time, the patient was referred with extensive hemorrhage and spontaneous face hematoma. Routine coagulation tests were rechecked and following to their abnormality, coagulation factor assays were performed again and vitamin K-dependent clotting factors were reduced and FEIBA successfully was administrated. Due to occurrence of hematoma patient was investigated for the factor 5 Leiden by activated protein C resistance test that showed patient was positive for this thrombophilic mutation. Since the patient has not any problem that can attribute to acquired form of VKCFD we performed routine and factor activity for her

father that was available. Her father had normal results of PT and APTT but vitamin K-dependent clotting factors were in lower limit of normal range.

Acquired VKCFD is a relatively common condition can results in severe hemorrhage. Acquired VKCFD may be observed in neonatal period as a temporal event [8, 9]. This diathesis is more common in patients with chronic liver disease but malnutrition, malabsorption and medications are other causes [8–10]. In this case, patient liver and gastric status was normal while most of vitamin K-dependent coagulation factors severely were reduced. The patient was not received any medication at the time of bleeding or recent past. In patient's serum sample, chylomicronemia was obvious and when triglyceride was measured, it was very high. Several studies were reported that variations in serum lipids including cholesterol and triglyceride could significantly affect vitamin K-dependent coagulation factors [9]. In the study of Maccallum et al., it was observed that protein C and protein S had significant variations in healthy individuals by increased level of cholesterol and triglyceride [8]. Similar finding were observed for other coagulation factors of this group. It was recommended that in vitamin K-dependent coagulation factors measurement, lipid profile of patient should take in consideration [10, 11]. Contraceptive pill or hormone replacement therapy are other factors can significantly affect these factors but our patient was not under this circumcision [8]. Serum vitamin K transport also can significantly alert by serum lipids mostly triglycerides [11]. All of these factors can affect vitamin K-dependent coagulation factors activation and therefore reduce their activity in blood stream [9, 11]. In the current patient, high serum lipids, the only factor that we found that can affect patient's coagulation factors and causes severe bleeding and hospitalization. This case emphasis this fact that high serum lipids not only affect in vitro measurement of vitamin K-dependent coagulation factors but also can cause severe life-threatening bleeds.

Keywords: Acquired VKCFD, Coagulation, bleeding, Serum lipids, Vitamin K

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Author Contributions

Vahid Niazi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Shahzad Soori – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Kamran Atarodi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Mohammad Hosein Esmaili – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Authors declare no conflict of interest.

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