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HEREDITARY COMBINED DEFICIENCY OF VITAMIN K–DEPENDENT CLOTTING FACTORS PRESENTING AS POSTOPERATIVE HAEMORRHAGE IN A SYRIAN ADOLESCENT: A LIKELY VKCFD TYPE 2 PHENOTYPE

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ABSTRACT

Hereditary combined deficiency of vitamin K–dependent clotting factors (VKCFD) is a rare autosomal recessive disorder characterized by reduced activity of factors II, VII, IX, and X despite normal vitamin K levels. We report a 17-year-old Syrian female who presented with impaired wound healing and haemorrhagic discharge following cervical rib surgery. Laboratory evaluation revealed markedly prolonged prothrombin time and activated partial thromboplastin time both corrected on mixing studies, and selective deficiency of vitamin K–dependent factors. Vitamin K levels were normal, excluding acquired causes. The patient experienced recurrent bleeding episodes including haematuria and epistaxis, successfully managed with plasma and recombinant activated factor VII. The absence of skeletal abnormalities, mild bleeding phenotype, and delayed onset suggest a VKCFD type 2 presentation. This case highlights the importance of early recognition, differentiation from acquired coagulopathies, and targeted replacement therapy to prevent life threatening haemorrhage.

KEYWORDS

Vitamin K-dependent clotting factors deficiency, factor V, factor VIII, factor X, factor IX, factor VII

LEARNING POINTS

- Consider vitamin K-dependent clotting factors deficiency in unexplained prolonged prothrombin time/activated partial thromboplastin time with normal vitamin K and combined factor deficiencies.
- Early recognition prevents catastrophic bleeding; vitamin K and factor replacement are lifesaving.
- Internists play a pivotal role in differentiating inherited from acquired coagulopathies.

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INTRODUCTION

Hereditary combined deficiency of vitamin K–dependent clotting factors (VKCFD) is a rare autosomal recessive disorder first described in the late 1970s[1,2]. It results from impaired γ carboxylation of vitamin K–dependent proteins, which is essential for calcium binding and coagulation activity. VKCFD is classified into two types: VKCFD1, caused by mutations in the γ glutamyl carboxylase (GGCX) gene, and VKCFD2, due to mutations in the vitamin K epoxide reductase complex subunit 1 (VKORC1) gene[3-6].

VKCFD1 often presents in infancy with severe bleeding and skeletal abnormalities, while VKCFD2 typically manifests later with milder bleeding and no skeletal involvement[4-9]. The clinical spectrum ranges from mucocutaneous bleeding to life threatening haemorrhage. Laboratory findings include prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), correction on mixing studies, and reduced activity of vitamin K–dependent factors with preserved factor V[1,2].

Management strategies include plasma, prothrombin complex concentrates (PCCs), and recombinant activated factor VII (rFVIIa)[5-7]. We present a case of VKCFD in a previously healthy adolescent female who developed postoperative haemorrhage after cervical rib surgery. The absence of skeletal abnormalities, mild bleeding phenotype, and delayed onset suggest a VKCFD type 2 phenotype.

CASE DESCRIPTION

A 17-year-old Syrian female horse rider with no significant past medical history, chronic illnesses, or prior medication use presented with a non-healing wound following cervical rib surgery performed via a supraclavicular approach. On examination, a noticeable swelling was observed in the supraclavicular area. The wound demonstrated impaired healing with haemorrhagic discharge localized to the cervical rib region *(Fig. 1)*. There was no personal or family history of bleeding disorders or coagulopathies.

Initial laboratory evaluation *(Table 1)* revealed mild anaemia

Parameter	Result	Reference range
White blood cell count, WBC ($\times 10^9$/l)	8	4–11
Red blood cell count, RBC ($\times 10^{12}$/l)	4.39	4.5–5.9
Haemoglobin. Hb (g/dl)	11.5	13.5–17.5
Mean corpuscular volume, MCV (fl)	82	80–100
Platelet count, PLT ($\times 10^9$/l)	500	150–400
Erythrocyte sedimentation rate, ESR (mm/hr)	13	0–15
Total bilirubin (mg/dl)	0.6	0.2–1.2
C-reactive protein, CRP (mg/l)	1.6	<5
Lactate dehydrogenase, LDH (U/l)	170	122-222
Calcium (mg/l)	8.5	8.5–10.2
Serum creatinine, Cr (mg/l)	0.7	0.7–1.3
Ferritin (ng/ml)	143	11–307
Vitamin B12 (pg/ml)	615	200–900
Alanine aminotransferase, ALT (U/l)	14	7–56
Aspartate aminotransferase, APS (U/l)	20	10–40
Rheumatoid factor, RF (U/ml)	5 (negative)	<20
Anti-smooth muscle antibody, ASMA	Negative	<1:20
Antinuclear antibody, ANA (HEp-2)	Negative	<1:80
Anti-phospholipid IgM (U/ml)	6	<10
Lupus anticoagulant, LA	Negative	<1:20
Serum protein electrophoresis, SPEP	Within normal limits	-

Table 1. Initial assessment.



Figure 1. Haemorrhagic discharge in the supraclavicular region.

(haemoglobin 11.5 g/dl), thrombocytosis (platelet count 500 $\times 10^9$/l), and otherwise preserved renal and hepatic function. Coagulation studies showed a markedly prolonged prothrombin time (5% activity, international normalized ratio 11) and prolonged aPTT (45 seconds), both corrected on mixing studies. Specific factor assays demonstrated severe reductions in factors VII (1%), IX (6%), and X (9%), with moderately reduced factor II (30%), preserved factor V (90%), and elevated factor VIII (229%). Fibrinogen, von Willebrand factor antigen, and factor XIII were within normal limits. Plasma vitamin K level by high-performance liquid chromatography was normal (2.2 ng/ml), excluding acquired deficiency *(Table 2)*.

The patient initially received blood transfusion and plasma, which temporarily controlled the bleeding. During her hospital course, she developed recurrent haemorrhagic manifestations, including wound site bleeding, gross haematuria, and epistaxis. These episodes were managed with repeated plasma infusions and recombinant activated factor VII administration, resulting in stabilization of haemoglobin and clinical improvement.

Preoperative cervical spine radiography demonstrated bilateral cervical ribs, more prominent on the right *(Fig. 2)*. A computed tomography scan of the chest, abdomen, and pelvis revealed no additional abnormalities.

Following discharge, the patient experienced two further episodes of wound site bleeding requiring readmission for plasma and factor VII support. With continued therapy, the wound gradually healed, and subsequent follow up showed resolution of bleeding episodes and overall clinical improvement without the need for ongoing treatment *(Fig. 3)*.

DISCUSSION

VKCFD is a rare but clinically significant cause of bleeding, especially in surgical settings. The disorder arises from impaired γ carboxylation of vitamin K–dependent clotting factors, a process essential for their activation[1,2]. Two molecular subtypes have been described: VKCFD1, due to GGCX mutations, and VKCFD2, caused by VKORC1 mutations. VKCFD1 often presents in infancy with severe bleeding and skeletal abnormalities[3-8], whereas VKCFD2 typically manifests later with milder symptoms and no skeletal involvement[4-6].

Our patient's presentation aligns with VKCFD2: she had no history of neonatal bleeding, no skeletal anomalies, and a relatively mild bleeding phenotype. The delayed onset in adolescence and absence of extra hepatic manifestations further support this classification[4-6].

The laboratory findings—markedly prolonged PT and aPTT, correction on mixing studies, and selective deficiency of vitamin K–dependent factors with preserved factor V—are diagnostic hallmarks[1,2]. The normal vitamin K level excluded acquired deficiency due to malnutrition, liver disease, or warfarin use[5-8]. Literature emphasizes that PT is usually more prolonged than aPTT, reflecting the short half-life of factor VII[1,2]. Vitamin K deficiency bleeding in infancy has also been described and must be distinguished from



Figure 2. Cervical spine radiograph, anteroposterior view, demonstrating preserved vertebral alignment. A cervical rib bud is noted at C7, large on the right and smaller on the left, consistent with bilateral cervical rib.



Figure 3. Healed wound.

hereditary VKCFD[8].

Genetic confirmation is considered the gold standard. Sequencing of GGCX and VKORC1 not only distinguishes VKCFD1 from VKCFD2 but also informs prognosis and family counselling[3-6]. Recent reviews highlight that GGCX mutations show variable responsiveness to vitamin K supplementation, whereas VKORC1 mutations often respond more consistently.

Management of VKCFD is individualized. Plasma and PCCs are effective for acute bleeding control, while recombinant activated factor VII (rFVIIa) has shown efficacy, particularly in patients with severe factor VII deficiency[6,7]. Our patient responded well to plasma and rFVIIa, with stabilization and resolution of bleeding episodes. Long term prophylaxis with vitamin K or intermittent rFVIIa has been reported in recurrent or life-threatening cases[6,7].

A recent systematic review identified approximately 60 genetically confirmed VKCFD patients worldwide, highlighting the broad clinical spectrum and genotype–phenotype correlations[10]. Clinical severity ranged from mild mucocutaneous bleeding to life threatening intracranial haemorrhage. About one third of cases were diagnosed in infancy, while others, like our patient, presented later in childhood or adolescence. Clinically significant bleeding generally occurs when factor levels fall below defined thresholds (FII <20%, FVII <20%, FIX <40%, FX <30%). Skeletal anomalies were strongly associated with VKCFD1, whereas VKCFD2 patients typically lacked extra hepatic features[3-9,10].

Test	Result	Interpretation
Prothrombin time, PT (% activity)	5 (INR 11)	Markedly prolonged
Activated partial thromboplastin time, aPTT (seconds)	45	Prolonged
Mixing study – PT (% activity)	80	Corrected → factor deficiency
Mixing study – aPTT (seconds)	29	Corrected → factor deficiency
Factor II (% activity)	30	Reduced
Factor V (% activity)	90	Normal
Factor VII (% activity)	1	Severely reduced
Factor IX (% activity)	6	Severely reduced
Factor X (% activity)	9	Severely reduced
Factor VIII (% activity)	229	Elevated (acute phase reactant)
Fibrinogen (mg/dl)	310	Normal
Von Willebrand factor Ag	Normal	Normal
Factor XIII (% activity)	70	Normal
Vitamin K (plasma, HPLC) (ng/ml)	2.2	Normal → excludes acquired deficiency

Abbreviations: INR, international normalized ration; HPLC, high-performance liquid chromatography.

Table 2. Coagulation studies and factor assays.

In summary, our case illustrates the diagnostic and therapeutic challenges of VKCFD. The absence of skeletal abnormalities, delayed onset, and mild phenotype support a VKCFD2 classification. Early recognition, comprehensive laboratory evaluation, and timely initiation of therapy are essential to prevent life threatening bleeding and long-term morbidity.

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