Case Report

Three-factorial Genetic Thrombophilia with Recurrent Thrombotic Events in a Saudi Patient: A Case Report

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Abstract

Thrombophilia is caused by several genetic and acquired factors. Existence of more than one genetic factor may increase the risk of developing recurrent thrombotic events. Here, we present a case of a 48-year-old male with a known history of deep venous thrombosis and a known mutation in factor V Leiden combined with mild protein S deficiency, who presented with a painful swelling in the left leg. Moreover, the patient had a history of diabetes, dyslipidemia and obesity. Prothrombin time and platelet count were within the normal range. The international normalized ratio and activated partial thromboplastin time were 3.21 and 36.7 s, respectively. The Doppler study showed a thrombus in the saphenous vein, and complementary genetic screening investigations revealed heterozygous mutation for prothrombin (G20210A). A diagnosis of multifactorial genetic thrombophilia was established. The patient was treated with warfarin, which resulted in significant improvement in the follow-ups, and at the time of reporting this case, there were no clinical or biological signs of thrombosis. The presence of multiple hereditary and acquired thrombophilic factors is a rare clinical presentation that requires close monitoring, for which a lifelong anticoagulation therapy should be discussed based on the clinical response of the patient.

Keywords: Factor V Leiden mutation, protein S deficiency, prothrombin gene mutation (G20210A), recurrent, thrombophilia

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INTRODUCTION

Vascular thrombosis is a major global health issue that has resulted in an increasing burden of morbidity and mortality as well as a significant rise in health-care expenditure. Thrombophilia, the increased tendency to develop thrombotic events in the blood vessels, has been extensively studied and found to be associated with multiple factors, with genetic and inherited factors being implicated in about half the cases.[1] Thromboembolic events often occur when multiple factors coexist, resulting in the disruption of the normal balance between the pro-coagulant and anticoagulant factors.

The genetic basis of thrombophilia was initially described by the discovery of inherited antithrombin III deficiency followed by the recognition of protein C and protein S deficiencies.[2] Subsequently, with the advent of DNA technology, activated protein C resistance and factor V Leiden (FVL) mutations constituted a major breakthrough as thrombophilic risk factors. In addition, a

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substitution mutation at the position 20210 of the factor II gene has been found to be associated with increased FII plasma concentrations, and hence an elevated risk of thrombosis. Mutations in FVL and FII G20210A represent significant risk factors for thrombosis (up to 2–5 folds), with an annual incidence of <0.5%/year for venous thromboembolism (VTE).[3] Deficiency of other natural anticoagulants leads to higher risks of thrombosis (5–10 fold) and >1% incidence of VTE.[4] The presence of multiple thrombophilic genetic defects in a single patient is possible, although very rare. Nonetheless, it is plausible that the risk of thrombosis expectedly increases with such combined genetic defects. Herein, we present a rare case of recurrent multifactorial thrombophilia with a heterozygous prothrombin (PT) gene mutation, FVL deficiency and protein S deficiency.

CASE REPORT

A 48-year-old male presented to our hospital with painful swelling in the left leg following a 10-h car trip. The patient was on oral metformin 500 mg once daily (OD) and atorvastatin 20 g OD to control diabetes mellitus and dyslipidemia, respectively; both conditions were well controlled.

He had a previous onset of deep venous thrombosis (DVT) for 4 years, and investigations had shown heterozygous FVL deficiency, as revealed by polymerase chain reaction-restriction fragment length polymorphism assays. The patient had been prescribed oral warfarin 5–6 mg OD. Six months after the first DVT attack, warfarin was discontinued for 4 weeks, after which further investigations were carried out that revealed a mild protein S deficiency. After the investigations, warfarin was restarted, but the patient stopped the medication 4 months later for no specific reason.

At the time of admission to our hospital, the patient was interviewed for other risk factors of venous thrombosis[5] and was found to have no history of prior surgeries or traumatic injuries of the legs/spine. Furthermore, there was no evidence of an active cancer, and the family history of thrombosis was unremarkable. On physical examination, the patient was found to be obese (Class I with a body mass index of 34.1 kg/m^2), and his respiratory rate was 13 breaths/min; heart rate was 77 beats/min; oxygen saturation in the ambient air was 99%; body temperature was 36.9°C and blood pressure was 129/86 mmHg. The lungs were clear, and cardiovascular examination revealed normal heart sounds. The liver and spleen were not palpable. A warm and tender swelling was observed in the mid-thigh that extended distally. The pulse was intact, with no varicose vein. Compared with the right leg, the left leg had increased circumferences above (left leg: 52 cm; right leg: 48.5 cm) and below (left leg: 45 cm; right leg: 39 cm) the knee.

Laboratory findings included normal blood cell count and renal and liver function tests. Coagulation studies showed a normal platelet count (295 k/μL) and activated partial thromboplastin time (36.7 s), but the international normalized ratio (INR) was 3.21 and free and total protein S was low (56.0%) controlled at 81.3%. The patient tested negative for cardiolipin antibody and beta-glycoprotein and lupus anticoagulant.

The Doppler study of the deep venous system of the lower limb revealed a complete occlusion of the saphenous vein by an iso- to hyper-echoic thrombus with no intravascular blood flow. The thrombus extended from the proximal to the distal segments of the vein, indicating a chronic thrombus [Figure 1]. In addition to the previous diagnosis of FVL deficiency and protein S deficiency, screening was carried out for other potential genetic factors that could affect coagulation, and heterozygous mutation for PT (G20210A) was found. The patient was diagnosed with a multifactorial genetic thrombophilia and was admitted to the Hematology division at the Department of Medicine for initiating the anticoagulant therapy.

The initial treatment included enoxaparin (8 mg subcutaneous injection, every 12 h) combined with warfarin (5 mg OD for 3 days). Subsequently, the warfarin dose was gradually increased until INR reached the therapeutic range, after which enoxaparin was discontinued. On the 10th day of admission, the patient was discharged with

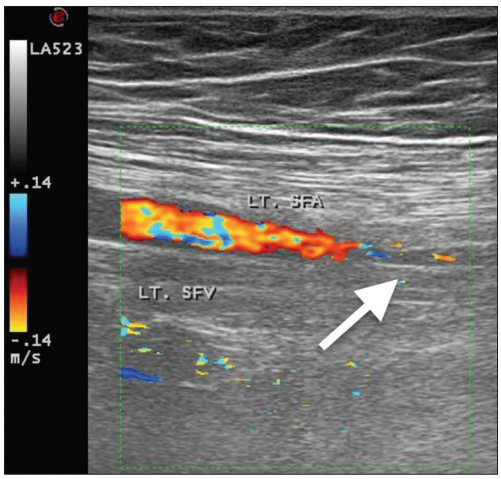

Figure 1: Doppler imaging of the lower limb showing complete occlusion (arrows) of the saphenous vein by an iso- to hyper-echoic thrombus with no intravascular blood flow

8 mg oral warfarin once per day. At the 1-week follow-up at the outpatient hematology clinic, the INR was 2.23 and clinical signs had improved remarkably. The patient was regularly followed up every 3 months to monitor the blood cell count, liver function, renal function and INR, and at the last follow-up at the time of reporting this case, there were no clinical or biological signs of thrombosis and the warfarin dose was maintained at 8 mg/day.

DISCUSSION

The current case represents a rare combination of three genetic factors, namely FVL deficiency, protein S deficiency and a heterozygous mutation of PT (G20210A), and to the best of the authors' knowledge, this is the first such case reported from Saudi Arabia. Several challenges contribute to augmenting the burden of multifactorial hereditary thrombophilia. First, using generalized recommendations for accurate testing may be difficult given the rarity of the condition, and hence, the true prevalence may be underestimated. Second, the risk of thromboembolic recurrence increases, particularly in males, with FVL deficiency.[6] Third, it may be possible that the interaction between more than one thrombophilic condition is multiplicative in increasing the risk of developing clinical manifestations rather than merely the sum of the impact from all deficient factors. Finally, a therapeutic challenge may emerge because, given the scarcity of similar cases, the management, including the medication type and dosage, is challenging, especially in the long term.

Multifactorial genetic thrombophilia could be associated with an increased risk of thrombosis compared with single-genetic defects.[7] Patients with a combined mutation of FVL and PT 20210 have an increased risk of spontaneous DVT in the lower and upper extremities as well as pulmonary embolization, and both the complications have a high recurrence rate.[7] Similarly, our patient had recurrent DVT due to the combined mutations. DVT was also a notable finding in two Caucasian patients with combined FVL and PT 20210 mutations who presented with VTE in the United States[8] and in one case in a series of 162 Lebanese patients.[9]

In terms of other serious complications, pulmonary embolism has been reported in a 19-year-old patient with type I antithrombin deficiency and a PT 20210 mutation [Table 1],[10] and recurrent pregnancy loss was observed in Saudi females with allelic polymorphisms in FVL and PT 20210 genes.[19] Similarly, in an early study from Germany, genomic mutations of PT and FVL were reported in 9.3% of women, and this increased the risk of VTE during pregnancy and puerperium.[20] In children, although the risk of stroke has been independently associated with the homozygous MTHFR mutations alone, recurrent stroke as well as a combination of three inherited mutations (PT G20210A, MTHFR and plasminogen activator inhibitor-1) has been recently reported in a Saudi child.[16] Likewise, the frequency of combined FVL and FII G20210A mutations was remarkably increased among Saudi neonates with stroke compared with healthy control adults with no history of thromboembolic events (odds ratio: 12.44, 95% confidence interval: 1.56–99.24).[21] These particular clinical pictures of recurrent miscarriage and pediatric stroke are to be added to the morbidity of multifactorial hereditary thrombophilia and should systematically raise suspicion of such conditions.

The existence of multifactorial hereditary thrombophilia cases highlights the relevance of relying on confirmative laboratory methods to quantitatively measure not only the presence of thrombophilia but also the degree of risk implied by multifactorial interactions. Despite the general consensus that tests of thrombosis should be deferred at the time of acute VTE episodes, genomic studies can be performed at any time. Nevertheless, there is an evidence of interference in the results of laboratory tests for distinct coagulation factors. Protein S activity may be underestimated by the coexistence of homozygous or heterozygous FVL mutations or even overestimated by co-administration of the direct Xa inhibitor rivaroxaban.[22] Both the interfering aspects were more prominent when using the PT time or Russell's viper venom time tests, while these errors were relatively resolved using the activated partial thromboplastin time to test protein S activity. In another perspective, Kyrle and Eichinger[23] suggested measuring the global markers of coagulation through D-dimer to detect patients with higher risks of recurrence. In the present case, protein S deficiency was diagnosed in a treatment-free time and 6 months after the resolution of the first DVT event.

In general, screening for hereditary thrombophilia should be considered in patients with recurrent VTE episodes, pregnant women at risk and individuals with a positive family history for thrombosis. An early study reported that 14 of 18 patients with more than one coagulation defect had a previous history of DVT and 5 of them experienced a PE onset.[5] In addition, the role of screening tests may extend beyond detecting recurrent episodes to include identification of thrombophilic traits in the asymptomatic family members of patients who could benefit from prophylactic interventions to reduce the risk of VTE, particularly in individuals with coexisting risks such as immobilization, pregnancy, puerperium and surgery.

Table 1: Summary of case reports that included patients with inherited thrombophilia of at least two thrombophilic genetic risk factors

Author(s) and year	Patient's demographics	Country	History	Manifestations	Coagulation defects	Diagnosis	Management
Two coagulation defects							
Brancaccio *et al*.[11]	27 years, male	Italy	Essential thrombocythemia	History of essential thrombocythemia concomitant with Budd–Chiari syndrome	Heterozygous FVL and PT G20210A mutation	Genotyping	An initial LMWH followed by warfarin
Bulut *et al*.[12]	A preterm (34 weeks) male infant	Turkey	Gestational DM and hypertension, fetal distress, maternal FVL and PT 20210 mutations without previous thrombotic episodes	Intrauterine growth retardation, bilateral RVT on prenatal ultrasound and insufficient respiratory effort on birth	FVL and PT 20210	Genotyping	LMWH (0.5 mg/kg/day), then RRT. Thrombosis persisted without improvement
Friedline *et al*.[8] (case 1)	36 years, male, caucasian	United States	A previous DVT	Swelling in the right leg	FVL and PT 20210	Genotyping	N/A
Friedline *et al*.[8] (case 2)	77 years, female, caucasian	United States	7 previous DVTs, hypertension, breast carcinoma	Bilateral lower extremity swelling	FVL and PT 20210	Genotyping	N/A
Laczika *et al*.[10]	19 years, female, white	Austria	Maternal PT 20210 mutation, a smoker patient receiving oral contraceptives	Chest pain, breathlessness. Acute unilateral PE by spiral CT	Type I antithrombin deficiency, PT 20210 mutation	Screening and genomic tests	High-dose IV unfractionated heparin followed by phenprocoumon
Rahman *et al*.[13]	40 years, male	Bangladesh	Recurrent DVT	Swelling in the left lower extremity	Protein C and Protein S	Genotyping	Enoxaparin 60 mg S/C, LMWH then warfarin 5 mg
Sturm *et al*.[14]	A preterm (30 weeks) male infant presented at 6 weeks of age	Germany	Fetal distress	Thrombotic complications at the site of venous catheters	Heterozygous protein C deficiency and a FVL mutation	Genotyping	No response to LMWH therapy (3 mg/kg) but improved with hirudin administration
Three coagulation defects							
Monsuez *et al*.[15]	50 years, female	Italy	Unremarkable	Painful edema of the left arm, hand and wrist	Heterozygous FVL, PT G20210A mutation and Protein S deficiency	High plasma D-dimer Positive screening tests for thrombophilia	An initial LMWH followed by warfarin
Alharbi *et al*.[16]	9 years, female	Saudi Arabia	Unremarkable	Weakness of the right hand and loss of grip	PT G20210A, MTHFR, Plasminogen Activator Inhibitor-1		Aspirin initially (5 mg/kg) then LMWH 1 mg/kg/day S/C
Brandenburg *et al*.[17]	29 years, female	Germany	Unremarkable	Acute myocardial infarction and intraventricular thrombus	FVL mutation, protein S deficiency and low antithrombin III	Screening tests	Phenprocoumon, ramipril 5 mg/day and enoxaparin. A significant improvement was achieved after 6 months
Four coagulation defects							
Pradhan *et al*.[18]	39 years, male	India	Unremarkable	Chest pain, breathlessness at rest CT pulmonary angiogram suggested bilateral pulmonary embolism	Protein C, S and anti thrombin deficiencies, hyper homocystenemia and FVL mutation	Screening and genomic tests	Streptokinase 2.5 lakh units followed by LMWH S/C and warfarin 5 mg OD

DM: Diabetes mellitus; FVL: Factor V leiden; LMWH: Low-molecular-weight heparin; MTHFR: Methylene tetrahydrofolate reductase; PE: Pulmonary embolism; PT: Prothrombin; RRT: Renal replacement therapy; RVT: Renal vein thrombosis; PT: Prothrombin; DVTs: Deep venous thrombosis; CT: Computed tomography; N/A: Not available; IV: Intravenous

The risk of DVT could possibly be higher when a third coagulation factor deficiency exists and the patient may be a candidate for a lifelong anticoagulation therapy. A three-factorial genetic predisposition (i.e., FVL, PT 20210 and protein S deficiency) to thrombosis was demonstrated in our patient, and another case has similarly been reported to cause a spontaneous DVT in the subclavian and internal jugular veins [Table 1].[15] Moreover, the presence of

four coagulation defects (deficiency of protein C, S and antithrombin as well as FVL mutation) was associated with the development of bilateral PE in a 39-year-old Indian patient.[18]

Besides these genetic factors, our patient had several acquired risk factors for thrombophilia, including diabetes, dyslipidemia and obesity, in addition to reduced physical activity following a car trip. Another example of the interplay between genetic and acquired factors is apparent in a Caucasian elderly woman who had a combined FVL and PT 20210 mutation and a history of breast carcinoma, hypertension and atrial fibrillation, which collectively contributed to her presentation with bilateral DVT.[8]

There is no difference in the initiation time, intensity and duration of treatment for thrombosis due to hereditary or acquired causes. The warfarin initial dose and the following dose increment along with monitoring INR levels were prescribed according to the published guidelines for the treatment of VTE.[24] The use of low-molecular-weight heparin (enoxaparin) was preferably suggested by the Society for Vascular Surgery[25] over vitamin K agonists to reduce the risk of developing postthrombotic syndrome after DVT. The decision regarding treatment duration should be based on the clinical response of the patient, yet the presence of three genetic coagulation defects might be suggestive of a lifelong anticoagulation therapy.

CONCLUSION

This report presents the first case of inherited thrombophilia with three genetic risk factors in Saudi Arabia. The incidence of recurrent DVT requires adequate screening of all congenital and acquired thrombophilia factors, as the risk of thrombotic events may be augmented with increased risk factors. Laboratory investigations for hereditary thrombophilia are warranted in cases of recurrent DVT (particularly in those aged <40 years), a positive VTE family history and pregnant women at risk, as adequate knowledge of prospective genetic risk factors will improve the diagnostic and preventive approaches of thrombophilia. There is need for novel technologies aimed at studying multiple genes in a single patient to determine the "individualized" and ethnicity-related risk factors in order to tailor the pertinent therapies accordingly.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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