

Recurrent Venous Thrombo-Embolism in a Young Adult Female: Case Report with Review of Literature

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Abstract

Venous thromboembolism (VTE), including both deep vein thrombosis (DVT) and pulmonary embolism (PE) is the third most common cardiovascular illness after acute coronary syndrome and stroke. VTE is a multi-causal disease that results from multiple interactions between genetic, acquired and circumstantial risk factors.

A 31 year old female patient presented with acute DVT at six weeks of her second pregnancy. She was managed accordingly with low-molecular weight Heparin throughout pregnancy; however, she developed multiple DVTs during the peri-partum period, after discontinuing the treatment for one week.

Thrombophilia screening revealed that she has two strong thrombophilic states: Factor V Leiden and Protein S deficiency, in addition to other circumstantial risk factors (Obesity and Dyslipidemia).

The combination of these two inherited diseases presents a challenge to the treating physician, especially during pregnancy.

In this article, we discussed this clinical case and the management plan that was followed with her till the current time with a review of literature in the same context.

We believe that addressing VTE as a regional public health problem should take a multi-dimensional approach targeting the epidemiology of the disease with implementation of cost-effective preventive and therapeutic programs.

Keywords: Venous Thrombo-Embolism; Deep Vein Thrombosis; Pulmonary Embolism; Congenital Thrombophilia; Anticoagulants

Introduction

Venous thromboembolism (VTE) is a condition including deep vein thrombosis (DVT) and pulmonary embolism (PE). It remains a common cause of mortality and morbidity in hospitalized or bedridden patients, as well as in healthy individuals. It is the third most common cardiovascular disease after acute coronary syndrome and stroke [1]. It has been estimated that 1 to 2 per 1,000 people are affected each year [2]. Approximately 1 out of 20 people develop a DVT during their lifetime [3]. Pulmonary embolism is considered third most common cause of hospital-related deaths and the most common preventable among them [4,5,6].

VTE is a multifactorial disease resulting from interactions between genetic, acquired, and circumstantial risk factors. Factor V Leiden leading to activated protein C-resistance is the most commonly occurring genetic risk factor for VTE. Inherited antithrombin, Protein C, and Protein S deficiencies are relatively rare [7,8].

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Case Report

A 31 year old Egyptian female, obese, nonsmoker, pregnant G2P1 with 6 weeks gestation, presented with left lower limb pain and swelling of 2 day duration. Her past history was not significant apart from a family history of deep vein thrombosis in mother. On clinical examination, her vital signs showed BP 124/88 mmHg, PR 90/min, regular, SpO₂ 98%, weight 122.6 kg. On local examination of left lower limb, there was mild swelling of the left calf muscle with tenderness. Urgent venous Doppler study of lower limbs showed acute deep venous thrombosis of left gastrocnemius vein. She was immediately started on a therapeutic dose of anticoagulation with low-molecular weight Heparin (LMWH) for 12 weeks along with elastic stockings. Her condition improved and a repeat venous Doppler 12 weeks later showed partially resolved thrombus in the left gastrocnemius vein.

While she was on LMW heparin during pregnancy, she underwent a thrombophilia screening which revealed the presence of two thrombophilias, firstly, a homozygous inherited Factor V Leiden mutation, detected by PCR DNA sequencing and secondly, a low protein S activity, determined by plasma clotting time-based assay. Other thrombophilia screen showed a normal protein C activity, normal antithrombin activity, normal homocysteine levels and negative antiphospholipid antibodies. Her echocardiography was found to be normal. She continued to be on LMWH till her delivery and abnormal progression of pregnancy was noted during the antenatal visits to obstetrics department.

At term, the patient was in her home country and she underwent elective caesarean section owing to her risk status and delivered a healthy baby. On subsequent OPD visit, it was learnt that she had discontinued the anticoagulant for a little more than 1 week following which there was recurrence of DVT symptoms. At that time, venous Doppler had revealed a DVT in the proximal right lower limb involving the external iliac, common and superficial femoral veins. She then continued to be on oral anticoagulation (Warfarin) guided by INR monitoring. During her subsequent visits; she had been diagnosed as having mild mixed dyslipidemia and vitamin D deficiency, for which appropriate treatment had been initiated.

After three months on oral anticoagulation therapy, a repeat venous Doppler showed progressive recanalization of the thrombosed right common and superficial femoral veins, popliteal vein and posterior tibial vein. Therapy with new oral anticoagulant (Rivaroxaban) was started. She was counselled regarding breast feeding and she opted for feeding her child with artificial formulas after consulting the pediatrician.

One month later, she developed some weight gain and on prolonged standing, she had recurrence of lower limb swelling with mild pain. Venous Doppler showed near complete recanalisation of right femoro-popliteal veins, therefore her symptoms were attributed to a post-thrombotic syndrome.

This patient had a recurrent unprovoked proximal venous thromboembolism, secondary to combined thrombophilia due to Factor V Leiden mutation and protein S deficiency.

Discussion

The pathophysiology of thrombosis composed of three main components, endothelial injury, venous stasis, and hypercoagulability (Virchow's triad) [9]. Hypercoagulability caused by thrombophilic disorders, can be inherited or acquired.

Inherited thrombophilia has been identified in 30% of idiopathic VTE patients [10-12]. Primary deficiencies of clotting inhibitors like antithrombin, protein C, and protein S have been associated with approximately 5-10% of all thrombotic events. The two most common hereditary thrombophilia are the factor V Leiden and prothrombin 20210 gene mutations [13-15].

Activated protein C (APC) is a natural anticoagulant which inactivates factor Va and factor VIIIa in the coagulation cascade. Factor V Leiden is a variant form of Factor V that cannot be inactivated by the APC, thereby causing hypercoagulability [16]. It is the most common genetic risk factor for VTE, found in 20–25% of VTE patients, in 50% of familial VTE7-9 and in 60% of pregnancy associated VTE [17]. The resistance to APC was discovered by Dahlback, *et al.* [18] in 1993 and the molecular defect was identified as a point mutation

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in Factor V by Bertina, *et al.* in Leiden (Netherlands), one year later. The FV Leiden mutation has autosomal dominant inheritance [17] in more than 90% of APC resistance cases [19] within complete penetrance. Homozygous individuals have a relative risk of 80-fold compared to 7-fold in heterozygous for thrombosis. Also homozygous experience VTE at a younger age (31 vs. 44 years) [20]. Regarding ethnicity, Jody, *et al.* [21] reported that FV Leiden occurred in 12-14% of the Arab nationalities, 3-15% of the European population and was extremely rare in African, Asian, and indigenous Australian populations.

Decreased levels or decreased function of protein S leads to reduced degradation of these factors and an increased propensity to venous thrombosis and it was found to be prevalent in 0.03-0.13% of the normal population [22-24]. About 0.8-3% of VTE are considered to be due to protein S deficiency [25,26]. It can be hereditary or acquired with three types being reported in hereditary deficiency by Comp., *et al.* [27] and Mannucci, *et al.* [28]. VTE is its most common manifestation [29], though stroke, aortic and coronary thrombosis, and renal vein thrombosis have also been reported [30-33].

The combination of FV Leiden and protein S deficiency has been estimated to be ~0.004%. A few cases with this combination have been reported from 1995-1997 [34-37]. Marie-Anne, *et al.* [38] in 1996, had commented that among cerebral venous thrombosis patients, factor V Leiden was almost always associated with other predisposing factors. Another study in 1998 by Mustafa, *et al.* [39] had suggested that among protein C or protein S deficient VTE patients, an increased incidence of a second thrombophilic defect, particularly factor V Leiden was found. Ivaylo, *et al.* [40] had reported in 1999 about a haemodialysis patient with recurrent A-V shunt thrombosis who was found to have a combination of APC resistance and acquired protein S deficiency.

Some researches demonstrated no correlation between APC resistance and protein S level [41], although Koeleman, *et al.* [42] had reported a high prevalence of this combination. There could have been possible misdiagnosis of APC resistance as protein S deficiency prior to discovery of APC resistance; nevertheless, this combination seems to be a very rare event [43].

Acquired causes of thrombophilia include protein S deficiency secondary to vitamin K deficiency or treatment with warfarin, pregnancy, systemic sex hormone therapy, liver disease and nephrotic syndrome, anti-phospholipid antibodies and certain chronic infections (for example Human Immuno-deficiency virus. During pregnancy, the protein S levels fall progressively [25] predisposing to recurrent VTE and/or fetal loss in pregnancy [44]. Also, acquired APC resistance (without FV Leiden) is another VTE risk factor and this is possibly due to high factor VIII levels or antiphospholipid antibodies [45,46]. Antiphospholipid antibodies (cardiolipin or Lupus Anticoagulant antibodies) are present in 2% of the population, and can also lead to a hypercoagulable state; however, these may be asymptomatic and could be detected in infections or administration of certain drugs like Hydralazine, Quinine or some antibiotics [11]. Another acquired factor is the presence of high homocysteine level, which may be seen in 10% of VTE patients can increase relative risk by 2- to 3-fold [21,47].

Genetic thrombophilia also interacts with environmental factors to increase VTE risk, for example, at least 50% of VTE in FV Leiden patients are triggered by additional predisposing factors [48]. The VTE risk increased with age with incidence being lower in the young and higher in the elderly [2,49]. Obesity (BMI > 30 kg/m²) increased VTE risk by 2.5-fold [50]. Another major risk factor was pregnancy, where trials have shown that during pregnancy and puerperium, FV mutation increased VTE risk by 8- to 52-fold, as compared with nonpregnant women without thrombophilia [51,52]. Major surgeries were complicated by VTE in 13%, suggesting an approximately 20-fold increase in risk [53]. Our patient was pregnant and also had undergone elective caesarean section which might have added to the risks and predisposed to another VTE episode. Air travel in a thrombophilic patient increased VTE risk by 14 to 16 fold [54,55]. In addition, a prior history of DVT still remains single most powerful risk marker, with an acute VTE incidence being 25% [56,57]. The recurrent episodes of VTE in our patient might be supported by this.

Conclusion

In our case, the patient had multiple thrombotic episodes due to a combination of two thrombogenic disorders. Patients risk profile included an inherited homozygous FV Leiden mutation, though protein S deficiency could have been an acquired condition rather than an inherited disorder, owing to her state of pregnancy. She also had other circumstantial risk factors favorable for VTE like obesity and

previous history of DVT. Since she had undergone a surgery, the post operative immobilisation and her postpartum state could also have been additional risk factors for the DVT recurrences. Hypercholesterolemia also could have contributed to the vascular damage. This suggested that the homozygous FV Leiden and protein S deficiency were together a very potent thrombophilic combination.

This proves that any suspected VTE patients should be assessed for all likely causes (genetic, acquired and circumstantial). The presence of one abnormality should not refrain us from searching for other underlying causes. The detection of such abnormalities has major consequences on the long-term prevention and management. The combination of FV Leiden and protein S deficiency in a pregnant female posed a challenge for the treating physician. Important concerns were regarding safety in pregnancy, further investigation for pulmonary embolism, termination of pregnancy, life-long anticoagulation therapy versus bleeding risks.

In at-risk population, prophylaxis is the most effective means to prevent DVT complications. Drugs which predispose to thrombosis (like combined oral contraceptives) should be avoided. Prophylactic anticoagulation should be started after bleeding risks assessment. Special consideration should be given to women who have unexplained recurrent pregnancy loss as future pregnancy outcomes can be improved by anticoagulant and antiplatelet therapy in underlying documented thrombophilia [58]. Nutritional replacement of folic acid, B12 and B6 in at-risk patients, may play a role in hypercoagulability related to homocysteine [59]. The place of screening for asymptomatic relatives of VTE patients continues to be under debate. It is essential to have informed consent of all concerned before any screening. Some argue that tests should be restricted to young women when they consider pregnancy or hormonal contraception as these are known risk factors.

The prognosis of hereditary thrombophilia will depend on early diagnosis, effective prophylaxis and effective management of any VTE. The prognosis of acquired thrombophilia largely depends on nature of underlying cause.

Therefore, VTE has to be recognized as a regional public health problem which can be tackled with a multi-dimensional approach towards the multicausal factors and implementing cost-effective preventive and treatment programs.

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