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CASE REPORT

Are Inherited Combined Thrombophilia Mutations a Causative or an Additive Factor in Recurrent Venous Thrombotic Accidents?

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SUMMARY

Background: **Inherited thrombophilia represents a prothrombotic disorder that predisposes to thrombosis.**
Methods: **We present a case of a 67-year-old female with a personal and family history of iterative thrombotic events. She was admitted in the Surgical Clinic at the age of 59, presenting the classical symptoms and signs for left lower limb deep vein thrombosis, confirmed by a venous Duplex Ultrasonography. This was the third episode of a venous thrombosis. Under anticoagulant treatment the evolution was good. The patient was advised to test for inherited thrombophilia mutations.**
Results: **Four years later, she experienced another episode of thrombosis. The patient tested positive for five of the most frequent mutations found in inherited thrombophilia.**
Conclusions: **Patients with recurrent venous thrombosis and positive family history for thrombotic events must be checked for thrombophilic conditions, inherited or acquired.**
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KEY WORDS

genetic tests, inherited thrombophilia, recurrent thrombosis

LIST OF ABBREVIATIONS

VTE - Venous thrombo-embolism
DVT - Deep vein thrombosis
PE - Pulmonary embolism
DUS - Duplex Ultrasonography
LMWH - Low molecular weight heparin
VKA - Vitamin K antagonists
PTS - Post thrombotic syndrome
Factor V Leiden - Factor V G1691A Leiden - G1691A FVL
Factor V HR2 - Factor V H1299R

Prothrombin G20210A - FII G20210A - G20210A prothrombin allele
C677T-A1298C MTHFR - C677T and A1298C of the methylenetetrahydrofolate reductase gene
4G/4G PAI-1 - 4G/4G polymorphism of the plasminogen activator inhibitor 1 gene
Factor XIII V34L - Polymorphisms of factor XIII V34 L gene
EPCR A1/A2 - Endothelial Protein C receptor A1/A2
ACCP - American College of Chest Physicians

INTRODUCTION

Venous thromboembolism (VTE), which covers deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious health problem for the individual and the health care system. In 2004, the estimated number of VTE-related deaths in Europe was over 370,000 [1]. Venous thrombosis is a disease with a complex and multifactorial pathogenesis. The development of this disease is a result of the interaction between environmental and genetic factors. Both acquired and inherited factors can determine thrombophilia, a condition that predisposes to thrombosis. Environmental/acquired factors such as surgery, cancer, immobilization, and obesity are often involved in VTE pathogenesis in older persons. Meanwhile inherited thrombophilia, a state that implies the presence of various genetic mutations, is cited as a predisposing factor for VTE in younger persons. Among these thrombophilic mutations, the most frequently cited are factor V Leiden, prothrombin G20210A, antithrombin III deficiency, methylenetetrahydrofolate reductase (MTHFR) mutations, protein C, and protein S deficiency [2]. A series of other genetic mutations which influence thrombotic processes are cited by different researchers and include 4G/4G plasminogen activator inhibitor 1 (PAI-1), factor V H1299R (HR2), factor XIII V34L, and endothelial protein C receptor (EPCR) A1/A2. Subjects presenting with one or more of these mutations are at a higher risk for VTE. Moreover, patients with homozygous mutations seem to have more serious symptoms and less favorable development. Compared to traditional/acquired risk factors for VTE, risk factors for inherited thrombophilia are relatively rare in the general population. The situation changes when the analysis is made in a VTE population, like the RIETE registry, where the general prevalence of inherited thrombophilia was about 7% in the total cohort [3].
When we refer to recurrent VTE, the most incriminating factors include a first unprovoked thrombotic event, male gender, old age, immobilization, cancer, and some inherited thrombophilia mutations (factor V Leiden, prothrombin G20210A) [4]. For this last topic, the literature is controversial regarding the influence of genetic mutations on the risk of VTE recurrence [3]. Determining the factors involved in VTE recurrence combined with the individual risk of bleeding is of utmost importance in determining the duration of anticoagulation therapy.
The aim of our paper was to present the personal and family history of a white female presenting with four thrombotic events manifested during a 24-year period. Our case tested positive for five heritable thrombophilic mutations.

CASE REPORT

We present a case of a Caucasian female patient who was followed regularly as an outpatient between 2010 and 2018. She was admitted in 2010 at the age of 59 for left lower limb DVT, to Surgical Clinic No. 1, Emergency County Hospital, Timisoara, Romania. The case was published with the agreement of the Ethics Committee of the hospital and the patient's written consent. At admission, the patient presented classical symptoms and signs for left lower limb DVT confirmed by a venous color Duplex Ultrasonography (DUS) that showed the presence of a left femoro-popliteal thrombus (Figure 1). Immediately after DUS confirmation, the patient was started on a therapeutic dose of subcutaneous low-molecular-weight heparin (LMWH).
The patient's medical history revealed that this was the third episode of venous thrombosis. The first episode was in 1994, at the age of 43, when the patient was admitted in another surgical unit. Here she was diagnosed, only on clinical basis, with superficial venous thrombosis of the left calf. She was dismissed after two weeks of treatment with topical anticoagulants and general antibiotic therapy. The second episode, left calf DVT, was in 2008, at the age of 57 and was likely provoked by prolonged immobility during a more than 12-hour bus trip. This episode was under diagnosed by a general practitioner/GP and apparently resolved without complications. Besides these two thrombotic events, our patient's medical history revealed a variety of diseases including gastric ulcer, cholecystectomy, hyperthyroidism with subtotal thyroidectomy followed by sudden menopause, fibrocystic breast disease, and hemorrhoid ligation. Apparently, none of these pathologies were relevant for the thrombotic events. The family history revealed a few thromboembolic accidents (Figure 2). After a five-day uneventful hospitalization and a cardiology exam that ruled out PE, the patient was discharged to continue on oral anticoagulants - vitamin K antagonists (VKA) for 6 months with an INR target between 2.0 and 2.5. After discharge, the patient received instructions about wearing compressive stockings, avoiding immobilization, and exposure to other thrombosis risk factors. Due to her personal and family history with recurrent thrombotic events, the patient was advised to undergo genetic testing for inherited thrombophilia mutations. She was seen as an outpatient for clinical and DUS evaluation at one, three, six, nine, and twelve months in the first year and afterwards yearly. Due to a relatively unsatisfactory clinical and DUS

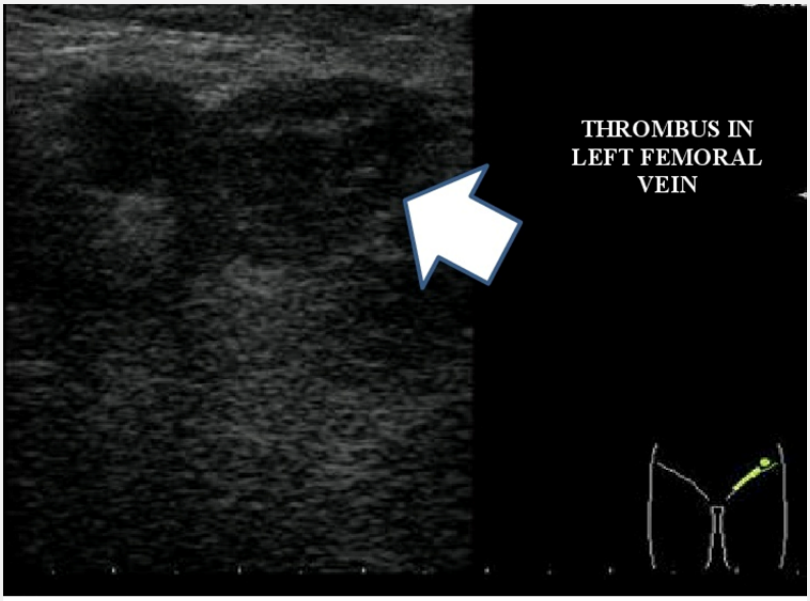

Figure 1. Femoral vein thrombosis Duplex Ultrasound image.

image development, the patient had to take VKA for one year. After discontinuation of VKA, the patient continued with small quantities of oral anticoagulant. Four years later, in 2014, the patient was referred for thyroidectomy following the diagnosis of recurrent multinodular goiter with compression phenomena. As part of the preanesthetic exam the patient was tested for eight thrombophilia mutations. Genetic tests revealed that she was heterozygous for factor V Leiden, C677T-A1298C MTHFR, factor XIII V34L, and homozygous for 4G/4G PAI-1. No mutations for prothrombin G20210A, factor V HR2, EPCR A1/A2 were found. In the same year, even though she was on a prophylactic dose of LMWH, on the fifth day after classical hemorrhoidectomy, the patient suffered a fourth thrombotic episode. This time she experienced a superficial venous thrombosis of the left upper limb, provoked probably by prolonged intravenous catheterization and confirmed by DUS. This episode resolved rapidly after 7 days on a therapeutic dose of LMWH followed by oral anticoagulant.

In light of the genetic test results, we decided to review her family history with a focus on DVT, PE, cardiovascular and cerebrovascular events, reproductive history, and cancer (Figure 2).

Between 2014 and 2017 the patient was diagnosed with Hashimoto's thyroiditis, Empty Sella syndrome, vitamin D deficiency and secondary hyperparathyroidism, and vitamin B12 deficiency, but was free from thrombotic events. Since 2016, both anticoagulant and antiplatelet therapies were recommended as treatment after a cardiology consult.

In 2017, the patient suffered an accidental trauma to the left calf with no thrombotic consequence, but with a large local hematoma secondary to combined anticoagulant and antiplatelet therapy. Two weeks after the trauma the patient experienced a subcutaneous hemorrhage on her right hand. On this occasion we decided to temporarily discontinue the antiplatelet therapy. Both the subcutaneous hemorrhage and the large persistent left calf hematoma had a favorable development. The last check-up, in October 2018, showed no added thrombotic event.

DISCUSSION

The first aim of the article was to draw attention to the fact that patients with recurrent venous thrombosis and positive family history for thrombotic events must be checked for inherited thrombophilia, even if they are over 50 years of age.

Genetic thrombophilia could become an issue especially in the context of an iterative VTE and in association with other risk factors. There are no uniform standards/recommendations for inherited thrombophilia testing. Our decision to recommend genetic thrombophilia testing was based on the fact that our case presented almost all the indications cited in the most comprehensive guide published by the British Committee for Standards

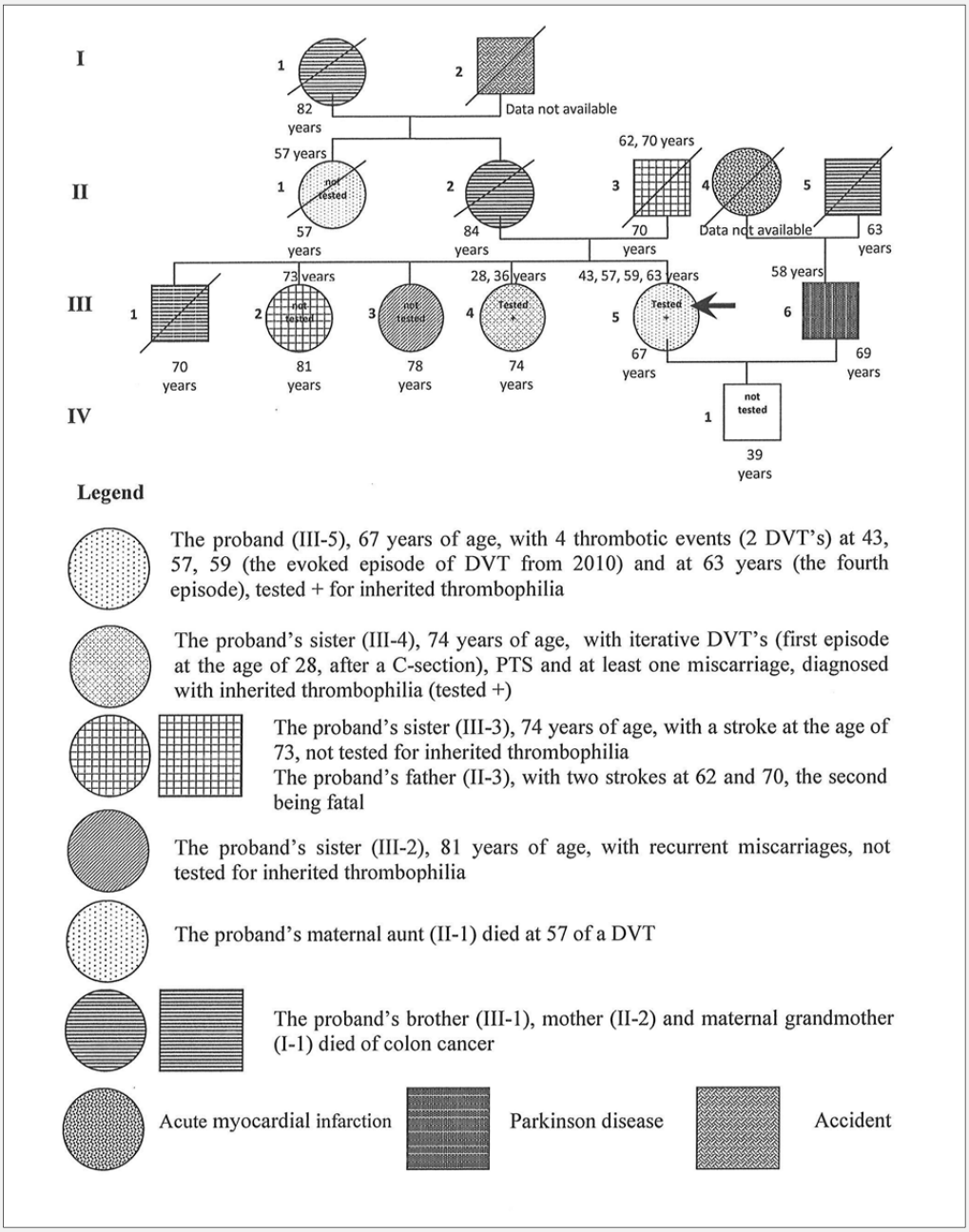

Figure 2. The patient's family history.

The proband (III-5) is indicated by an arrow.

in Haematology [5]. Our patient presented with recurrent VTE events and family history of thrombotic events (Figure 2). The first thrombotic episode was registered under the age of 50 and two of the three thrombotic episodes were apparently unprovoked/associated with weak provoking factors [5,6].

The first thrombotic episode was registered at 43 years of age and was unprovoked. On this occasion she denied oral contraceptive use, immobilization, recent surgery or trauma, or exposure to other traditional VTE risk factors. The second episode was likely a provoked one, a traveler's thrombosis.

Despite the fact that while managing the third thrombotic episode we did not have proof for genetic thrombophilia, we decided to extend the time for VKA treatment to one year mostly because of an unsatisfactory clinical and DUS development. This decision made was based on the recommendation of The American College of Chest Physicians (ACCP) guidelines, 8th edition that states that "the risk of recurrence after stopping therapy is largely determined by two factors: (1) whether the acute episode of VTE has been effectively treated; and (2) the patient's intrinsic risk of having a new episode of VTE" [7].

Four years after the third thrombotic episode, in 2014, our patient tested positive for five thrombophilia gene mutations. Accordingly, she was found to be heterozygous for factor V Leiden, one of the most encountered thrombophilia mutations among VTE patients, 25% in both situations, first unprovoked and recurrent episodes of venous thrombosis [3]. This heterozygous status was listed as present in 3 to 8 percent of the European and U.S. Caucasian population [8]. This mutation is known as activated protein C resistance and produces a mild hypercoagulable state. Heterozygous carriers of factor V Leiden, mostly those < 45 years, were found to have a four-fold increased risk of first VTE event [8]. Another thrombophilia mutation found in our case was the compound heterozygosity of C677T-A1298C MTHFR. This compound mutation induces an increase in homocysteine levels, a condition which increases the risk of VTE up to four times, especially in women [9]. The results pertaining to the real influence of this compound mutation on VTE are controversial [10]. As far as our case is concerned, we can hypothesize that this genetically determined hyperhomocysteinemia could be doubled by a secondary increase in homocysteine level on the first registered thrombotic event due to a thyroid hormone imbalance. Nevertheless, in the case of associated thrombophilic mutations the risk for VTE events increases [10].

The second aim of the article was to emphasize the importance of general measures and precautions in order to minimize the risk of VTE in the general population, but even more in those with thrombophilia. The presence of one or more inherited thrombophilia mutations may become important in estimating the need both for primary, but especially for secondary prophylaxis, as in our case [7]. Our patient suffered the fourth thrombotic episode during a postoperative period, under LMWH therapy. The episode was most likely provoked by a peripheral venous catheter held in place for five days. Often patients with VTE and inherited thrombophilia may have additional risk factors that increase venous-clot formation as in our case due to immobility from prolonged travel in the second episode and a remnant peripheral venous catheter in the fourth episode.

CONCLUSION

The present article reports a particular case of inherited thrombophilia, manifested by four episodes of thrombotic events in twenty years, diagnosed with genetic thrombophilia after the age of 50. Even though the recommendations for inherited thrombophilia testing are for younger patients aged below 40 - 50, this case, knowing that the patient had thrombophilia, would have required increased vigilance for secondary prophylaxis for recurrent VTE.

Declaration of Interest:
Nothing to declare.

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