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Educational Case Report

Recurrent deep vein thrombosis in a young patient of African descent: challenging the prevailing stance on the significance of MTHFR C677T mutation

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Abstract

Background: Although numerous gene variations, such as those in the methylenetetrahydrofolate reductase (MTHFR) gene, have been implicated in an increased risk of venous thrombosis, current recommendations do not advocate genetic testing if there is no clinically meaningful association with thrombosis. **Case Presentation:** A 30-year-old male patient presented with left lower limb swelling of two days with prior history of deep vein thrombosis and superficial thrombophlebitis. His left lower limb was grossly swollen. Doppler study showed thrombosis of left common femoral, superficial femoral and iliac veins and work up for inherited thrombophilia was negative except detection of MTHFR C677T mutation. **Conclusion:** In spite of the great controversy regarding the strong association between MTHFR C677T mutation and venous thromboembolism, it is worth considering genetic testing as part of work-up for inherited thrombophilia in young patients, particularly of African descent, if they have recurrent deep vein thrombosis with no obvious risk factors.

BACKGROUND

Venous thrombosis (VT) is a complex illness due to the interaction of hereditary and acquired prothrombotic causes, as well as environmental influences [1]. The most common acquired risk factors for VT are oral contraceptive use, puerperium, paralysis, surgery, extended immobility, fractures, cancer, and the antiphospholipid antibody syndrome [2]. Genetic factors account for around 60% of deep vein thrombosis (DVT) cases and notable thrombophilic defects include mutation in the methylenetetrahydrofolate reductase (MTHFR) gene, factor V Leiden G1691A (FVL) mutation, and prothrombin G20210A (PT 20210 gene) mutation respectively [3].

The MTHFR gene contains two frequent polymorphisms, C677T and A1298C, which cause the enzyme's activity to be reduced and the level of homocysteine to be elevated. Numerous investigations have suggested that these two polymorphisms may be connected to DVT brought on by hyperhomocysteinemia [4–7]. The MTHFR C677T mutation is particularly prevalent in specific ethnic and geographical populations. The frequency of this mutation is estimated at 1% to 2% in black people; whereas, 20% to 40% of white and Hispanic individuals in the United States are heterozygous for MTHFR C677T [8].

Although numerous gene variations, such as those in the methylenetetrahydrofolate reductase (MTHFR) gene, have been implicated in an increased risk of thrombosis [9], current recommendations do not advocate genetic testing if there is no clinically meaningful association with thrombosis [10]. Here, we describe a case of young male patient of African descent who experienced recurrent deep vein thrombosis and was found to have heterozygous MTHFR C677T gene mutation.

CASE PRESENTATION

A 30-year-old Ethiopian male patient presented with left lower limb swelling of two days, which was getting painful while he was walking. He had previous history of deep vein thrombosis of the left lower limb three years before his current presentation and he took anticoagulant (warfarin) for three months. He had also superficial thrombophlebitis on his right leg seven months prior to his current presentation; for which he received anticoagulant (rivaroxaban) for three months. He is a bank accountant and claims an average mobility with occasional prolonged sitting. He had no constitutional symptoms like fever, night sweating, loss of appetite or weight loss. He did not have cough, hemoptysis or bowel habit changes. He had no history of cigarette smoking or alcohol consumption. He did not give a family history of venous thromboembolism and malignancy. He had no history of chronic medical illness and no prior history of surgery.

On physical examination, he had blood pressure of 130/80 mmHg, pulse rate of 80 beats per min, respiratory rate of 18 breaths per min, oxygen saturation of 97% with room air, grossly swollen left lower limb with significant discrepancy from the right lower

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Table 1. Summary of laboratory investigations.

Laboratory tests	Units	Results	Reference ranges
White blood cell count	cells/μl	7.6×10^3	$4–10 \times 10^3$
Hemoglobin	g/dl	13.4	12–16
Platelets	cells/μl	263×10^3	$150–450 \times 10^3$
Erythrocyte sedimentation rate	mm/h	2	<15
HbA1c	%	5.2	<5.7
Aspartate aminotransferase	U/l	29	<35
Alanine aminotransferase	U/l	25	<35
Creatinine	mg/dl	0.8	<1.3
HIV	–	Negative	–
aPTT	seconds	39	20–38
PT	seconds	11	10–14
Factor V Functional Activity	%	67.40	62–139
Protein C, Functional Activity	%	77	62–139
Protein S, Functional Activity	%	95	77–143
Antithrombin Functional Activity	%	82	80–120
Cardiolipin Antibody, IgM	MPL	8.97	<12.5
Cardiolipin Antibody, IgG	GPL	8.38	<15
Cardiolipin Antibody, IgA	APL	7.45	<12
Beta 2 Glycoprotein, IgM	SMU	6.07	<20
Beta 2 Glycoprotein, IgG	SGU	1.01	<20
Beta 2 Glycoprotein, IgA	SAU	2.10	<20
Prothrombin gene (G20210A) mutation	–	Not detected	–
Factor V Leiden (R506Q) mutation	–	Not detected	–
MTHFR gene (C677T) mutation	–	Heterozygous mutation detected	–

Abbreviations: aPTT—Activated Partial Thromboplastin Clotting Time; PT—Prothrombin time; HbA1c—hemoglobin A1c; ESR—Erythrocyte Sedimentation Rate; HIV—Human Immunodeficiency Virus; IgM—Immunoglobulin M; IgG—Immunoglobulin G; IgA—Immunoglobulin A.

limb. There was no remarkable finding on the respiratory and cardiovascular systems.

He was investigated with Doppler venous ultrasound of the left lower limb, which revealed distension of the left common femoral, superficial femoral and iliac veins with extensive thrombosis along with incompressibility and absence of blood flow. On laboratory tests, complete blood count, liver enzymes, renal function tests, glycated hemoglobin, and coagulation profile were within normal ranges. He tested negative for HIV. Laboratory tests for antiphospholipid antibody syndrome and inherited thrombophilia were non-remarkable except the detection of heterozygous MTHFR gene (C677T) mutation on real time PCR mutation analysis (Table 1). Determination of serum homocysteine level was planned after the detection of heterozygous MTHFR gene (C677T) mutation, but it was not done due to unavailability of the test and financial constraints. Further investigations including fecal occult blood test and abdominopelvic ultrasound were not revealing any positive finding and age specific cancer screening tests including tumor markers were not done because the patient was young with no clinical features or family history suggestive of malignancy.

He was treated with rivaroxaban 15 mg PO two times daily BID for the first 21 days and then he was continued with the same medication at a dose of 20 mg PO daily for the first 03 months followed by secondary prevention strategy at a dose of 10 mg PO daily. He had significant improvement of the leg swelling. He did not have short term or long term complications of deep vein thrombosis and there were no bleeding events due to the anticoagulant use.

DISCUSSION

Deep vein thrombosis (DVT) risk is heightened by conditions like obesity, cancer, pregnancy, estrogen-containing drugs, major surgery, and hospitalizations. Occupations in transportation, air travel, confined spaces, and sedentary office jobs all increase the risk of deep vein thrombosis (DVT) and genetic testing can identify some inherited factors that increase the likelihood of DVT in susceptible individuals [11]. The relative sedentary office job of our patient and the MTHFR C677TT mutation detected on genetic testing might have contributed to the development of recurrent DVT.

An important risk factor for unexplained DVT could be underlying malignancy. At the time of presentation with unexplained DVT, the majority of patients with undetected malignancy show some clinical abnormalities suggestive of underlying malignancy. It doesn't seem acceptable to perform extensive cancer screening on all patients who present with unexplained DVT [12]. Based on a nested case–control study of patients who were registered with the RIETE (Registro Informatizado Enfermedad ThromboEmbólica) registry, a risk score for occult cancer diagnosis in VTE patients was created. Older age (>70 years old), chronic lung illness, thrombocytosis, and anemia were all factors that were independently linked to an elevated likelihood of occult cancer detection [13]. Our patient did not have any clue or risk factor for underlying occult malignancy and detailed investigations including tumor markers were not done.

Antithrombin III, protein C, protein S, factor V Leiden, the prothrombin G20210A allele, and MTHFR mutations are among the genetic causes of venous thromboembolism [14]. Our patient tested negative to all of these coagulation studies except the MTHFR C677T mutation, which has been linked to DVT in some studies [15, 16], although they have not been significantly correlated in other studies [17, 18].

A reduced MTHFR enzyme function can result in elevated homocysteine levels, which increase the risk of developing venous thromboembolism or cardiovascular diseases; however, it does not always do so, particularly with consumption of food fortified

with folic acid [8]. The homocysteine level is not determined in our patient; nonetheless, the probability of having recurrent deep vein thrombosis may be possible due to the MTHFR C677T mutation, which might result in elevated homocysteine levels, as the patient was not taking food fortified with folic acid.

The MTHFR gene mutation was the most prevalent thrombophilic defect in a retrospective analysis of 115 patients with thrombophilia who were between the ages of 16 and 50. This was followed by factor V Leiden mutation, the presence of antiphospholipid antibodies, and the prothrombin G20210A gene mutation. The findings of this analysis suggested that young adult patients presenting with thrombotic episodes may have some significant thrombophilic defects, such as gene mutations [1]. In line with the findings of this analysis, our patient was a young adult who was found to have a thrombophilic defect (MTHFR C677T mutation).

It is worth noting that there are two important limitations in this case report. The first limitation is the absence of determination of homocysteine levels, which are expected to increase in patients having reduced MTHFR enzyme function and they are also associated with increased risk of developing venous thromboembolism or cardiovascular diseases. The second limitation is related to testing for thrombophilia, which was done while the patient was on anticoagulation and this might have affected some of the profiles.

CONCLUSION

In spite of the great controversy regarding the strong association between MTHFR C677T mutation and venous thromboembolism, it is worth considering genetic testing as part of work-up for inherited thrombophilia in young patients, particularly of African descent, if they have recurrent deep vein thrombosis with no obvious risk factors.

AUTHORS' CONTRIBUTIONS

G.S. was involved in the conceptualization of the case report and prepared the initial draft of the manuscript. A.A. and C.A. were involved in the revision of the initial manuscript. All the authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

No funding organization was involved in this case report.

DATA AVAILABILITY

Supporting data is available with the corresponding author and it will be accessible upon reasonable request.

ETHICS APPROVAL

The case report meets ethical guidelines and adheres to the local legal requirements.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of his case details.

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