Hyperhomocystetenemia, MTHFR Mutation Presenting as Unprovoked Pulmonary Embolism

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ABSTRACT

Introduction: For MTHFR as with homocysteine testing, no official guidelines exist as to who should be tested. Homozygosity for the MTHFR C677T mutation has been associated with an increase in blood clotting together with plasma homocysteine increase and DVT occurrence risk.

Case report: A 28 year young male patient presented with complaints of sudden onset breathlessness for 5 days. The episodes of breathlessness were associated with diffuse anterior chest pain. There was no history of leg pain, cough, sputum, hemoptysis, fever. No history of prior hospitalization, trauma, surgery and immobilization could be elicited from the patient. He was a non smoker with no other comorbidities. On presentation his pulse rate was 120 per minute, respiratory rate was 22 per minute, blood pressure 146/92 mm Hg, temperature 98.8 ° F, SpO_2 of 94% at room air. His general physical examination was unremarkable.

Conclusion: Although it has been observed that elevated homocysteine levels are a common finding in patients with cardiovascular disease and thrombosis, its role in its pathogenesis is still under evaluation. Homozygosity for the MTHFR C677T mutation has been associated with increased homocysteine levels. Testing for this mutation is an important parameter in thrombophilia workup of patients with unprovoked VTE.

Keywords: Hyperhomocystetenemia, MTHFR Gene, Pulmonary Embolism, Unprovoked.

INTRODUCTION

Venous thromboembolism (VTE) is the third most common cardiovascular disease with an annual overall incidence of 100-200 per 100,000 individuals.[1] Acute Pulmonary Embolism (PE) is a life threatening presentation of VTE. Majority of deaths resulting from PE remain undiagnosed. Older patients (>40 years) are at an increased risk compared with younger patients and the risks approximately doubles with each subsequent decade.[2] Various risk factors predispose to VTE (Table 1).

Computed tomography (CT) angiography has become the method of choice for imaging the pulmonary vasculature in patients with suspected PE.[3]

Hyperhomocysteinemia is an important risk factor for ischemic heart disease, deep venous thromboembolism, PE and stoke.[4] The regulation of plasma levels of homocysteine requires both environmental factors (folic acid and vitamin B12 intake) and hereditary components.[5] Mutations in genes encoding enzymes like methylene tetrahydrofolate reductase (MTHFR) C677T, A1298C and methionine synthase reductase (MTRR) A66G may contribute to the risk of developing HHCY and pulmonary embolism.[6]

CASE REPORT

A 28 year young male patient presented to our tertiary care hospital in the out-patient department with complaints of sudden onset breathlessness for 5 days. The episodes of breathlessness were associated with diffuse anterior chest pain. There was no history of leg pain, cough, sputum, hemoptysis, fever. No history of prior hospitalization, trauma, surgery and immobilization could be elicited from the patient. He was a non smoker with no other comorbidities. On presentation his pulse rate was 120 per minute, respiratory rate was 22 per minute, blood pressure 146/92 mm Hg, temperature 98.8 ° F, SpO_2 of 94% at room air. His general physical examination was unremarkable.

Routine investigations were within normal limits. Cardiac enzymes (CK-MB, hs-troponin I) were negative. Electrocardiogram showed sinus tachycardia. D-dimer levels were 2290 ng/ml DDU. 2 dimensional ECHO showed right atrium, right ventricle dilatation with left ventricular ejection fraction (60%). Thrombosis at the junction of popliteal and segmental veins was found in lower limb doppler studies.

Computed tomography pulmonary angiography with intravenous contrast showed filling defect suggestive of thrombosis at bifurcation of right and left pulmonary arteries and almost all segmental branches (Fig 1).

Initial coagulation profile which included prothrombin time, activated partial thromboplastin time, international normalized ratio (INR), antiphospholipid antibodies, protein C and S and anti-thrombin III levels was within normal limits. Factor V Leiden and prothrombin gene mutations

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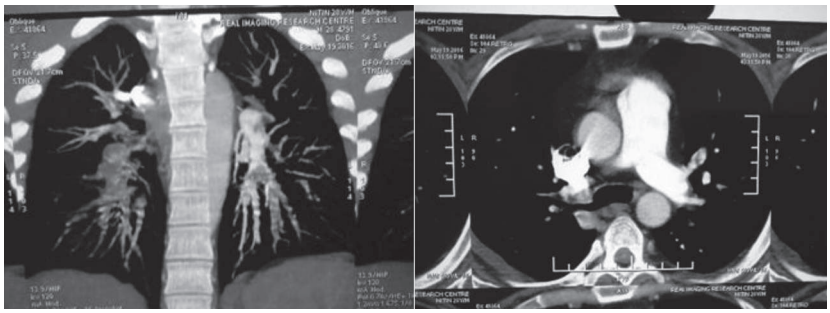

Figure-1:

Predisposing risk factor	Relative risk weighting
Thrombophilia	High
History of VTE	High
Malignancy	High
HIV infection	High
Advanced age (>60 yrs)	Moderate
Chronic cardiac insufficiency	Moderate
Obesity (BMI >30kg/m^2)	Moderate
Oestrogen therapy	Moderate
Pregnancy and postpartum period	Minor
Nephrotic syndrome	Minor
Varicose veins	Minor

Table-1: VTE risk factors[2]

1. Anticoagulant deficiencies:
Protein C activity
Free protein S antigen
Anti-thrombin activity
2. Antiphospholipid antibodies
Lupus anticoagulant
Anti-beta-2-glycoprotein-I antibody
Anti-cardiolipin antibody
Elevated homocysteine concentration
3. Factor V Leiden mutations; prothrombin mutations
4. Elevated factor VIII activity
5. Elevated lipoprotein(a) concentration
6. Methylene tetrahydrofolate reductase (MTHFR) mutations

Table-2: Comprehensive thrombophilia testing[8]

1. Thromboembolic disease
2. Stroke
3. Aneurysm
4. Peripheral artery disease
5. Migraine
6. Hypertension
7. Recurrent pregnancy loss
8. Male infertility

Table-3: Positive association of MTHFR mutation[9]

were not detected. Additional coagulation studies showed elevated serum homocysteine levels (90umol/L), normal vitamin B12 and folic acid. Genetic testing found patient to be positive for homozygous for the MTHFR G677T variant. The patient was thrombolysed with recombinant tissue plasminogen activator in view of acute cor-pulmonale and deteriorating clinical condition. He was discharged on oral warfarin after overlap with Fondaparinux, adjusting the dose to maintain an INR of 2-3.

DISCUSSION

Venous thromboembolism tends to occur due to a combination of endogenous, genetic and environmental risk factors.[5] The most common factors for VTE are hospitalization, cancer and surgery. Although PE is considered a disease of the old, studies have revealed the increasing incidence of PE in young individuals.[6] Pregnancy, oral contraception, trauma, venous compression syndromes, inflammatory bowel diseases and intravenous drug abuse have been reported to be typical risk factors in young population.[6,7]

Our patient had none of the above mentioned risk factors. Thrombophilia testing for blood clotting risk factors is an important part of the evaluation of causes and risk factors in young people with newly diagnosed DVT or PE (Table 2).

Homocysteine is a sulfur-containing amino acid absent in naturally occurring dietary sources. It is a chemical produced on breakdown of amino acid methionine in the body. Elevated homocysteine levels are associated with increased risk of atherosclerosis, CAD and Stroke. (Table 3)

Homocysteine can be measured in blood through a simple routine test. We used the laboratory established cut off values of 60 umol/L for severely elevated homocysteine levels, between 13-60 umol/L for borderline elevated, and less than 13 umol/L as normal.[2]

Several studies in patients with venous thrombosis failed to demonstrate an association between MTHFR C677T polymorphism and increased risk of venous thrombotic disease[10,11] whereas other studies have reported a positive association.[12] For MTHFR, as with homocysteine testing, no official guidelines exist as to who should be tested. Homozygosity for the MTHFR C677T mutation has been associated with an increase in blood clotting together with plasma homocysteine increase and DVT occurrence risk.[12]

CONCLUSION

Certain studies have suggested that elevated homocysteine levels may double up the risk of developing venous thrombosis. Although it has been observed that elevated homocysteine levels are a common finding in patients with cardiovascular disease and thrombosis, its role in its pathogenesis is still under evaluation. Homozygosity for the MTHFR C677T mutation has been associated with increased homocysteine levels. Testing for this mutation is an important parameter in thrombophilia workup of patients with unprovoked VTE.

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