

Dual Genetic Abnormality in the Coagulation Pathway as a Cause of Familial Thrombophilia

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Abstract

Inherited deficiency of certain factors is responsible for increased tendency to vascular thrombosis; however two genetic defects in the coagulation pathway may coexist and cause recurrent thrombosis. Previously studies of thrombophilia have focused on the identification of single gene defects with the concept that familial thrombophilia is a single gene disorder. Now it has become accepted that familial thrombosis in protein C-deficient families is caused by co-segregation of one or more additional genetic factors that increase the risk of thrombosis.

Co-existence of two or more genetic abnormalities increases the risk of thrombotic tendencies in affected persons. Simultaneous presence of factor V Leiden and deficiency of protein C results in higher risk of thrombosis. We report two such cases with additional analysis of the family tree highlighting that dual abnormality results in higher penetrance of the disease among family members.

Introduction

Inherited deficiency of certain factors may be responsible for increased tendency to vascular thrombosis; however two genetic defects in the coagulation pathway may coexist and cause recurrent deep venous and arterial thrombosis. During the past twenty years, the study of thrombophilia has focused mainly on the identification of single gene defects that could explain the segregation of the thrombophilia in the affected families. The concept underlying this notion was that familial thrombophilia is a single gene disorder. Now it has become accepted that familial thrombosis in protein C-deficient families is caused by co-segregation of one or more additional genetic factors that increase the risk of thrombosis.

Co-existence of two or more genetic abnormalities increases the risk of thrombotic tendencies in affected persons. It has been observed that thermolabile mutant form of the enzyme; methylene tetra-hydrofolate reductase (MTHFR) gene is not independently associated with thrombosis.¹ However co-existence of hyperhomocysteinemia has been shown to increase the risk of thrombosis in patients with factor V Leiden.² Similarly, simultaneous presence of factor V Leiden and deficiency of protein C may result in higher risk of thrombosis.³

Case History

A 52-year old male presented with complaints of acute pain in the right foot. Local examination revealed pedal oedema and absent pulsations in the right dorsalis pedis and posterior tibial arteries. Rest of the systemic examination was normal. Routine haematological investigations, blood sugar, renal and liver function tests and X ray of chest were within normal limits. A Doppler study revealed evidence of significant disease in the right anterior tibial artery, and the right dorsalis pedis and posterior tibial arteries showed no flow. Per-operative findings revealed about one cm clot in the posterior tibial artery. The

patient underwent a right distal popliteal bypass grafting but the procedure failed. Then an embolectomy was attempted, but was unsuccessful. Finally, an above knee amputation had to be undertaken.

The patient recovered and remained asymptomatic for the next 18 months during which the patient did not take any anticoagulants. Thereafter he presented with complaints of swelling of the left foot for 2-3 days. He was diagnosed to have deep venous thrombosis (DVT), however he refused hospitalization and treatment. Two weeks later, he was rushed to the emergency room with complaints of sudden onset of breathlessness. At that time he had a blood pressure of 110/70 mm Hg and a pulse rate of 120/min. Local examination of the left leg revealed a tender and swollen calf and thigh and Homan's sign was positive. Examination of the chest revealed tachypnoea and basal crackles on the right side. The electrocardiograph showed right axis deviation and sinus tachycardia. X ray chest was suggestive of a pulmonary infarct involving right lower lung. Doppler study was suggestive of left popliteal venous thrombosis with extension into the common femoral vein. He was treated with inj. heparin and oxygen inhalation. The patient recovered and was put on oral anticoagulation with acetocoumarin and advised to maintain INR between 2.5 to 3.0. After 6 months acetocoumarin was stopped and patient was put on low molecular weight heparin for 2 weeks and protein C and S levels were checked. He was again restarted on acetocoumarin thereafter. His protein C level (antigenic assay) was found to be only 5% (normal: 70-140%). He was found to have acquired protein C resistance - Factor V Leiden (PCR based assay). His protein S and anti-thrombin III levels, collagen profile including antiphospholipid antibodies, and HBsAg, HIV and anti HCV were normal.

Eight months later, patient's son, a 24 year- old male presented with complaints of swelling of the right foot and calf for 10-12 days. The Doppler study was suggestive of DVT with partial re-canalization of the right lower limb venous system. He was put on treatment with intravenous anticoagulation. His protein C levels were found to be only 3% of normal (70-140%) and he was also detected to have factor V Leiden. The patient is on treatment with acetocoumarin and maintains an INR of approximately 2.5.

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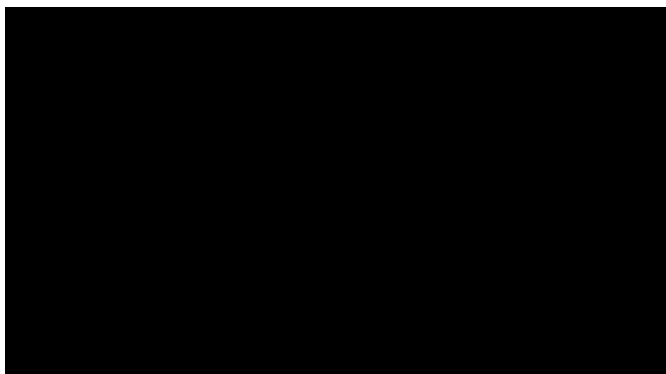


Fig. 1 : Pedigree analysis shows that several family members had a thrombophilic state. Solid boxes indicate the two index cases. Empty boxes with arrows indicate cases that had suffered from at least one episode of deep venous thrombosis in the past.

Keeping in view the familial association in the case, a detailed family study was done as shown in the pedigree chart (Figure 1).

Discussion

Inherited thrombophilia is a genetically determined tendency to venous and sometimes arterial thrombosis that develops in young patients and tends to be recurrent. So far, various genetic abnormalities which have been accepted as risk factors for venous thrombosis include protein C deficiency, protein S deficiency, antithrombin deficiency, dysfibrinogenemia, factor V Leiden mutation, and more recently, the 20210 A allele of the prothrombin gene. Besides this, hyperhomocysteinemia can be caused by genetically or nutritionally determined abnormalities of the homocysteine metabolism. In an Indian study, in young patients presenting with thrombosis, at least 34% of them had a demonstrable cause for thrombophilia with a high prevalence of variant MTHFR C677T.⁴ Presence of additional genetic defects and clinical risk factors are important co-determinants of thrombosis risk.¹

Protein C deficiency is an autosomal dominant disease with variable penetrance. It has been observed that the risk for thrombosis is variable among protein C deficient families. Koeleman et al analyzed DNA of 48 unrelated probands with clinically dominant protein C deficiency and found that factor V Leiden mutation was present in nine of these 48 symptomatic protein C deficient probands. They felt that thrombophilia in clinically manifest protein C deficient families, is probably

caused by the combined action of heterozygous protein C deficiency and presence of factor V Leiden. It was found that penetrance of thrombophilia was significantly higher in carriers of a both gene defects (73%) than in carriers of single gene defect (36% and 10%). It was found that thrombosis-free survival was significantly shorter in those carrying two gene defects as compared to those with one or no gene defect.⁵ Similarly co-existing hyperhomocysteinemia has been shown to increase the risk for thrombosis in patients having factor V Leiden.² Likewise, co-inheritance of the 20210A allele of prothrombin gene appears to increase the thrombotic risk in patients with other forms of thrombophilia such as those due to deficiency of protein C, protein S or anti-thrombin III.⁶

These findings support the concept that familial thrombophilia may occur due to one or more gene defects and that thrombotic manifestation are significantly higher in those with more than one gene defect. The presence of dual genetic abnormality in the coagulation pathway in our patients resulted in higher penetrance of thrombophilia in various family members. This may have clinical implications for the patients who may need to achieve a higher INR and long-term and even lifelong anticoagulant therapy.

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