Coexistence of Factor V Leiden and Hyperhomocysteinemia

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Abstract

A 76-year-old male patient with coexistence of factor V Leiden and hyperhomocysteinemia is reported. Since the patient had a recurrent venous thrombotic condition and factor V Leiden was positive, he was tested for other genetic risk factors. The patient's homocysteine level was found to be elevated. There were no findings indicating presence of other genetic risk factors. Identification of genetic defects which result in an increased tendency to thrombosis has important implications for the patients and also for their families.

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Introduction

Genetic variations which lead to an increased tendency to thrombosis must be investigated in patients who have recurrent venous thrombotic events, venous thrombosis at an early age, venous thrombosis unrelated to any recognized stimulus or a family history of proven venous thrombosis (1). People with more than one heritable thrombophilic condition carry an increased thrombotic risk (2).

Hyperhomocysteinemia results from genetic defects of methionine metabolism and inadequate intake of folate, vitamin B_6 and B_{12} (3,4). Previous studies suggest that hyperhomocysteinemia may be a risk factor for venous thromboembolism (VTE), but that this constitutes a relatively weak risk factor for VTE unless other genetic defects coexist (5,6). Activated protein C resistance, a defect usually caused by a single point mutation in the gene coding for coagulation factor V, is referred to as factor V Leiden. Although factor V Leiden increases the risk of thrombosis, many individuals with factor V Leiden may not show signs of thrombosis unless they have additional factors, such as deficiency of protein S or protein C.

We report this patient as an interesting example of a heritable thrombophilic condition.

Case Report

A 76-year-old male was admitted to our hospital with dyspnea and palpitation. The patient had been suffering from dyspnea during exercise and fatigue for the past six years. Due to a sudden attack of dyspnea at rest eight months ago, he had been admitted to another hospital. and had been diagnosed as a case of chronic thromboembolic pulmonary hypertension. His chest x-ray had

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shown cardiomegaly. Hypoxemia and hypocapnia were reported in his arterial blood gas analysis. The perfusion scan disclosed perfusion defects, whereas ventilation scan was normal. In echocardiographic-doppler evaluation, right ventricular enlargement and pulmonary hypertension (mean PAB: 78 mmHg) were found, whereas left ventricular functions were reported as normal. Anticoagulation therapy had been administrated. Because the patient had a history of recurrent thromboembolic disease, testing for thrombophilia was also considered. It was found that he was heterozygous for factor V Leiden. Prothrombin G20210A was normal. The patient had been on anticoagulation therapy during the past six months but in the last two months, he had taken his medicines irregularly.

On admission the patient was found to have a temperature of 37°C, a heart rate of 115 beat/min, and a respiratory rate of 32 per minute. His blood pressure was 120/70 mmHg. Chest auscultation revealed decreasing respiratory sounds over the right hemithorax. Pretibial edema was positive. Other systemic findings were normal. A chest x-ray demonstrated cardiomegaly with left costodiaphragmatic blurring. On blood gas analysis, pH was 7.49, $PaCO_2$ 28.9 mmHg, PaO_2 43 mmHg and HCO_3 22.5 mmol/L. Electrocardiography showed right ventricular hypertrophy. Right ventricular enlargement and pulmonary hypertension (mean PAB:60 mmHg) were found in a second echocardiographic-doppler evaluation, while left ventricular functions were normal. A Doppler ultrasonography showed deep venous thrombosis. This condition was attributed to irregularity in the anticoagulant therapy irregularly as well as to the existence of a recurrent venous thrombotic event. Anticoagulant therapy was started. The patient did not accept to undergo right-heart catheterization and pulmonary angiography. Since he was thought to have a recurrent venous thrombotic event and since factor V Leiden was positive, we tested the patient for other genetic risk factors. Activity of antithrombin III, protein S, protein C, protein S antigen and prothrombin G20210A levels were normal. However, homocysteine level measured in the fasting state was 23.9 μmol/l (normal range 0.00 to 12.00 μmol/l). Renal function and serum vitamin B_{12} and folate levels were normal. We recommended long-term oxygen therapy in addition to anticoagulant therapy.

Discussion

The haemostatic changes leading to thrombosis are the result of interactions between genetic and environmental factors. Testing for thrombophilia is not usually considered after an episode of VTE in an elderly patient, while identification of a heritable thrombophilic condition is attempted when unprovoked venous thrombosis occurs in a patient with a positive family history or in a young patient with children or siblings, especially female children or women of child-bearing age (1). Our patient had recurrent venous thrombotic events and also was positive for factor V Leiden. In general, patients who have combinations of thrombophilia require consideration for long-term treatment with oral anticoagulant therapy. Therefore we tested our patient for other genetic risk factors.

Heterozygosity for factor V Leiden or prothrombin G20210A are the most common heritable thrombophiliac conditions (7-9). On the other hand deficiency of the natural anticoagulants antithrombin, protein C, protein S or hyperhomocysteinaemia and existence of combined defects are uncommon.

Factor V Leiden was found positive but prothrombin G20210A was normal in our patient. Factor V Leiden is found in 20-50% of patients presenting with a first episode of venous thromboembolism (10). Heterozygous carriers have been reported to have a three to eight-fold increased risk of venous thromboembolism and homozygotes an 80-fold increased risk (10-12), but this type of information on heritable thrombophiliac conditions are limited. Although the risk of thrombosis is increased by factor V Leiden, many individuals show no signs of thrombosis unless they have another genetic defect (13,14). Mandel et al suggested that factor V Leiden was also important in determining which patients with homocystinuria developed thrombotic complications (15). Hyperhomocysteinemia leads to an approximately two to five-fold increased risk of venous thromboembolism when the homocysteine levels exceed 18.5 μmol/l (5,16,17). The homocysteine level of our patient was 23.9 μmol/l, indicating an increased risk for venous thromboembolism. Hyperhomocysteinaemia has a number of genetic causes including abnormalities of β-cystathionine synthase and methylene tetrahydrofolate reductase (18). Additionally, inadequate intake of folate, vitamin B_6 and B_{12} is important. Especially the milder forms of hyperhomocysteinemia are difficult to diagnose and these forms are potentially remediable by dietary manipulation (19,20). No nutritional deficiencies were identified in our patient and we were not able to investigate a number of genetic causes for hyperhomocysteinemia because of financial difficulties.

Homocysteine is thought to produce a thrombogenic effect by damaging the endothelium (2). Rodgers et al found an *in vitro* effect of homocysteine on factor V activation and inhibition of thrombomodulin-dependent protein C activation (21). Combination of this defect with other heritable thrombophilia defects increases the risk of thrombosis Our patient is an interesting case from this point of view. Mandel et al reported that enviromental risk factors increased the tendency to thrombosis among patients who have factor V Leiden and homocystinuria (15). But we were not able to identify any enviromental risk factors in our patient.

Since there is no reliable data on the risk of recurrent venous thromboembolism in patients with heritable defects, the duration of anticoagulant therapy is debatable. The rate of recurrent venous thromboembolism after discontinuation of anticoagulant therapy was reported to be higher in factor V Leiden heterozygotes (22,23). However, other studies have

yielded conflicting results (24,25). It is recommended that when there is a persisting thrombotic risk factor such as cancer or an identified high risk thrombophilic defect, the duration of anticoagulant therapy should be extended (1). Our patient suffered from pulmonary hypertension and had a low cardiac reserve, thus a recurrent thrombotic event could prove to be fatal for him. Additionally, he had more than one genetic defect. Therefore long-term treatment with oral anticoagulant therapy was considered.

We proposed to investigate thrombophilic genotype in the family but were not able to obtain the consent of the family members. There is no evidence to support the administration of thromboprophylaxis to asymptomatic family members found to have a thrombophilic genotype, but they should be counseled about the signs and symptoms of thromboembolism and should be made aware of the importance of seeking medical attention at an early stage (1). We informed the patient and his relatives about these details. In summary, identification of genetic variations which result in an increased tendency to thrombosis has important implications for the patients and also for their families in helping to guide management and in avoiding further thrombosis. In addition, patients with heritable thrombophilic conditions need to be evaluated before surgical, medical or obstetrical procedures.

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