

Combination of factor V Leiden and MTHFR mutations in myocardial infarction

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Identifying patients who are at high risk of suffering myocardial infarction can be done by determining risk factors or by the adoption of molecular genetic testing for inherited thrombophilia. We report a case of myocardial infarction at a young age. The patient complained of dyspnea (stage III) and a burning pain of severe intensity that radiated to the left retrosternal side, but was not associated with palpitations or diaphoresis. A number of biochemical parameters were normal except for an elevated creatinine phosphokinase (CPK) level. Genetic testing revealed the subject to be heterozygous for both the factor V Leiden and MTHFR C677T polymorphisms. The combination of these two mutations may be a high risk factor for myocardial infarction. Genetic screening for inherited thrombophilia in young patients, especially in the presence of a common risk factor, may be useful for primary thromboprophylaxis and in asymptomatic relatives of patients.

Myocardial infarction (MI) is an important clinical problem because of its large contribution to mortality. The most important and common risk factors for MI include hypertension, hypercholesterolemia or dyslipidemia, diabetes mellitus, and smoking. Some recent studies have also demonstrated the important relationship between prothrombotic genetic markers and MI.¹ For example, several reports on the association between the factor V Leiden mutation and MI in young patients are available.^{2,3} Other studies, however, have cast doubt on the role of certain thrombotic genetic markers and MI. One such study found no strong evidence to support an association of the C677T methylenetetrahydrofolate reductase (MTHFR) polymorphism and coronary heart disease in different populations.⁴ This report concerns the case of a young subject who had a heterozygous defect in the factor V Leiden gene as well as C677T MTHFR polymorphism. The combination of these mutations, along with his past smoking habit, is suspected to be the probable cause of his MI.

CASE

A previously healthy 48-year-old Tunisian male was

admitted to our cardiology department with oppressive chest pain. The patient complained of dyspnea (stage III) and a burning retrosternal pain that was severe in intensity and radiated to the left side but was not associated with palpitations or diaphoresis. Currently a nonsmoker, he had been a 1-pack-per-day smoker. His blood pressure was 140/80 mm Hg and pulse rate was 80/min; other clinical parameters were stable. The patient had a positive family history of hypertension.

Biochemical studies, electrocardiogram, and echocardiography were performed. A coronary angiogram revealed completely normal coronary arteries. Platelet, fibrinogen, prothrombin, protein S, protein C, and antithrombin III levels were all found to be normal. Tests for antiphospholipid and anticardiolipin antibodies were negative. Cardiac enzymes were measured: the troponin level was normal (<0.01 ng/mL); however, the creatine phosphokinase was elevated to 253 IU/L (normal, 10-195 IU/L). A complete genotype analysis for inherited thrombophilia was carried out on total DNA extracted from blood. PCR was used with a commercial kit (ThromboType plus; Hain Lifescience, Nehren, Germany). The test for the prothrombin G20210A and MTHFR A1298C mu-

tations were negative, but the patient was found to be heterozygous for factor V Leiden and positive for C677T MTHFR mutation.

MI was diagnosed and treatment was instituted. Anticoagulation therapy with aspirin, atenolol (Hypoten) and captopril (Lopril) was effective. The patient was followed up in the cardiology department and continued to do well at home 3 years after discharge.

DISCUSSION

The identification of patients who are at high risk of suffering MI can be done by assessing risk factors or by molecular genetic testing for inherited thrombophilia. This is of great importance, particularly for asymptomatic first-degree relatives of MI patients. Genetic disorders of coagulation proteins, in general, have important effects on thrombus formation, thrombolysis, or both. The most commonly encountered gene polymorphisms may increase the risk for ischemic heart disease.⁵ Specifically, the role of thrombophilia in the pathogenesis of MI has been intensely studied in recent years and is still debated. For example, the association between the homozygous 677T T MTHFR polymorphism and MI have been examined, but the results of studies demonstrated that the role of MTHFR in MI was not well established.⁶ Moreover, other studies have failed to establish a definitive role of certain inherited thrombophilias in MI.⁷ Recently, however, large-scale multigenic association studies have revealed that the C677T MTHFR polymorphism is a significant risk

factor associated with the prevalence of MI.^{8,9} Similarly, while a retrospective study did not demonstrate an increased prevalence of the heterozygous factor V Leiden mutation in patients with MI,¹⁰ other studies have reported that the risk of suffering an MI was increased by 40% in heterozygote carriers of the factor V Leiden mutation.¹¹ A synergistic effect between atherogenic risk factors and thrombogenic mutations in the pathogenesis of MI has also been suggested.⁶ In particular, the concomitant presence of smoking and factor V Leiden mutation was found to increase the risk of MI in young men.^{12,13} Therefore, in our patient, MI may have been a consequence of the synergism between inherited thrombophilia and cigarette smoking. Indeed, genetic testing for prothrombotic mutations might be important in selecting patient management, such as prophylactic anticoagulation therapy or institution of measures for avoidance of behavioral risk factors, such as smoking.¹⁴

In conclusion, it is likely that the combination of factor V Leiden mutation and the C677T MTHFR polymorphism, in the presence of conventional risk factors, increased the risk of MI in our case. Genetic typing could prove useful in identifying subjects who require prophylactic treatment so as to avoid such cardiovascular events.

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