Myocardial Infarction in a 35-Year-Old Man With Homocysteinemia, High Plasminogen Activator Inhibitor Activity, and Resistance to Activated Protein C

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Our specific aim was to examine the interface between risk factors for atherosclerosis, thrombosis, and hypofibrinolysis in a previously healthy 35-year-old male who had sustained a recent myocardial infarction. By angiography, the right, left main, and left anterior descending coronary arteries were smooth-walled, widely patent, and free of significant obstruction; the circumflex exhibited total, probably thrombotic occlusion of the distal large second marginal branch. The patient was found to have prothrombotic high homocysteine (46.4 μmol/L), prothrombotic resistance to activated protein C (ratio, 1.47), and hypofibrinolytic high plasminogen activator inhibitor (PAI-Fx) activity (54 U/mL). He was homozygous for the 677C → T; A → V mutation in the methylenetetrahydrofolate reductase (MTHFR) gene causing homocysteinemia, heterozygous for the mutant factor V Leiden gene causing resistance to activated protein C, and heterozygous for the 4G/5G polymorphism in the PAI-1 promoter gene causing high PAI-Fx. Other major risk factors for coronary artery disease included previously undiagnosed adult-onset diabetes, high triglycerides (291 mg/dL), and low high-density lipoprotein (HDL) cholesterol (26 mg/dL). The patient's prothrombotic status (homocysteinemia and resistance to activated protein C) and hypofibrinolysis (high PAI-Fx) apparently facilitated occlusive coronary artery thrombus formation and retention. Prothrombotic factors and hypofibrinolysis appear to play important pathogenetic roles in premature myocardial infarction. In patients with severe premature coronary artery disease, we suggest that interactions between prothrombotic factors, hypofibrinolysis, and hyperlipidemia-atherosclerosis be regularly evaluated, since such interactions may have ramifications for the outcome of short- and long-term secondary prevention. Moreover, in patients with heritable prothrombotic factors or hypofibrinolysis, it should be important to optimize lipid and lipoprotein cholesterol levels with the goal of stabilizing coronary plaques to reduce the likelihood of plaque rupture and thrombosis.

PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) is the major inhibitor of fibrinolysis,[1] is associated with coronary artery stenosis,[2] predicts the reoccurrence of myocardial infarction in young men,[3] and is pathoetiologic for osteonecrosis, causing venous thrombosis in the head of the femur.[4] A common, heritable 4G/5G single nucleotide insertion/deletion polymorphism in the PAI-1 promotor region has been identified[5] that is related to circulating PAI levels[6] and to hypofibrinolysis. The prevalence of the 4G allele is higher ($P < .05$) in patients with myocardial infarction before age 45 years than in controls.[5]

Homocysteinemia is a significant independent, usually heritable, prothrombotic risk factor for atherothrombotic cardiovascular, cerebrovascular, and peripheral vascular disease.[7,8] Subjects homozygous for methylenetetrahydrofolate reductase (MTHFR) usually have high serum homocysteine levels.[9] The common homozygous mutation in the MTHFR gene is associated with a threefold increase in the risk for premature cardiovascular disease.[9]

The most common heritable cause of thrombosis is resistance to activated protein C,[10,11] primarily associated with an increased risk of venous thrombosis, but also with arterial thrombosis.[12,13]

Platelets play an important role in arterial thrombosis, with an association between the $P1^{A2}$ polymorphism of the glycoprotein IIIa gene and acute coronary thrombosis, particularly in patients with coronary events before age 60 years.[14,15]

In the current study, we assessed the interface between prothrombotic factors (high homocysteine and resistance to activated protein C), hypofibrinolysis (high PAI activity), and atherosclerotic factors (mature-onset diabetes, high triglycerides, and low high-density lipoprotein [HDL] cholesterol) as etiologic factors for premature myocardial infarction in a 35-year-old previously healthy man.

SUBJECT AND METHODS

Patient and Study Protocol

The patient, a 35-year-old Egyptian male physician, was referred to us after sustaining an acute inferior myocardial infarction while exercising. To assess the etiology of his myocardial infarction, we measured a panel of atherosclerotic and prothrombotic risk factors. These included the fasting lipid profile,[16] lipoprotein (a) [Lp(a)],[16] PAI activity (PAI-Fx[16]), serum homocysteine and methylmalonic acid,[8] resistance to activated protein C,[10,11] anticardiolipin antibodies,[17] the lupus anticoagulant, antigenic and functional proteins C, S, and antithrombin III,[18] fasting blood glucose, and hemoglobin A_{1c}. We also assessed mutations in the MTHFR gene,[9] insertion/deletion (4G/5G) polymorphisms in the promotor region of the PAI gene,[5,6,19] and the presence of the mutant factor V Leiden gene.[10,11] Studies were also made of the $P1^{A2}$ polymorphism of the gene encoding glycoprotein IIIa.[14,15]

RESULTS

Prior to the acute myocardial infarction at age 35, the patient, a non-obese, nonhypertensive nonsmoker, had been healthy and asymptomatic, not known to have diabetes, and free of overt thrombotic events.

On coronary angiography at the time of the myocardial infarction, the right, left main, and left anterior descending coronary arteries were smooth-walled, widely patent, and free of significant atherosclerotic obstruction. The right coronary

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artery was dominant among the major coronary arteries. However, the circumflex system exhibited total, probably thrombotic occlusion of the tortuous distal large second obtuse marginal branch.

When evaluated by our group 6 weeks after the acute myocardial infarction, the patient was found to have hypofibrinolysis with high PAI activity[4,11,16-18] with heterozygosity for the 4G/5G polymorphism in the PAI gene,[5,6,19] prothrombotic homocysteinemia[7,8] with homozygosity for the MTHFR gene mutation,[9] and prothrombotic resistance to activated protein C with heterozygosity for the mutant factor V Leiden gene[10,11] (Table 1). The prothrombotic lupus anticoagulant test was borderline abnormal. Although the patient had an abnormal dilute viper venom time (DVVT) of 46.2 seconds (upper-normal limit, 38.8 seconds), his activated partial thromboplastin time (26 seconds) was normal (upper-normal limit, 33 seconds) and his 50/50 mix DVVT was normal (36.1 seconds; upper-normal limit, 38.8 seconds). The platelet genotype was $P1^{A1/A1}$, which is not associated with a high prevalence of acute coronary events.[14,15]

Other major risk factors for coronary artery disease included previously undiagnosed mature-onset diabetes, high triglycerides, and low HDL cholesterol, all in the absence of central obesity (Table 1).

Total and low-density lipoprotein cholesterol levels were entirely normal, 139 and 55 mg/dL, respectively. He was normotensive and had normal Lp(a) (20 mg/dL),[16] normal anticardiolipin antibodies (IgG 20 GPL and IgM 1 MPL),[17] normal antigenic and functional proteins C (118% and 125%), S (126% and 122%), and antithrombin III (105% and 115%).[18]

DISCUSSION

Fibrin deposition is a consistent feature of atherosclerotic plaques.[20] High PAI-Fx probably leads to increased fibrin deposition via inhibition of fibrinolysis, encouraging plaque formation and growth.[1-3,5,6] Since acute myocardial infarction is often associated with thrombosis at a ruptured atherosclerotic plaque, high PAI-1 probably contributes to a prothrombotic state that increases the likelihood of thrombosis and occlusion of coronary arteries.[5,6] Our patient's heterozygosity for the 4G/5G polymorphism in the PAI-1 gene promotor probably accounted for the high PAI-Fx and hypofibrinolysis, since the 4G allele of the PAI-1 promotor is associated with higher PAI-1 activity.[5,6] The patient's high PAI-1[5,6] was only one of six major independent risk factors[21] (high PAI-1, high homocysteine, resistance to activated protein C, high triglycerides, low HDL cholesterol, and mature-onset diabetes) for the premature myocardial infarction. Our patient also had two heritable prothrombotic traits, homocysteinemia[7,8] with homozygosity for the MTHFR gene mutation[9] and resistance to activated protein C with heterozygosity for the mutant factor V Leiden gene.[10,11] The 677C → T; A → V mutation in the MTHFR gene responsible for the thermolabile phenotype and elevated homocysteine levels is associated with a threefold increase in the risk for premature cardiovascular disease.[9] Although resistance to activated protein C[10,11] is primarily associated with venous thrombosis, it can increase the risk for arterial thrombosis[12,13] and has been shown to contribute to thrombosis in homocysteinemic patients.[22] We postulate that heterozygosity for the mutant factor V Leiden trait can increase the risk of arterial thrombosis in the presence of other concurrent prothrombotic factors and hypofibrinolysis, as in the current patient.

Table 1. Coagulation, Lipid, and Diabetic Abnormalities and Gene Mutations

Assay	Level	Normal Value	Gene Mutation
PAI activity (U/mL)	54.0	<26.9	Heterozygous 4G/5G
Homocysteine (μmol/L)	46.4	<16.2	Homozygous MTHFR
Resistance to activated protein C (ratio)	1.47	>1.81	Heterozygous mutant factor V Leiden
HDL cholesterol (mg/dL)	26	>35	—
Triglyceride (mg/dL)	291	<200	—
Fasting glucose (mg/dL)	156	<105	—
Hemoglobin A_{1c} (%)	7.6	<6.4%	—

Our patient was at substantially increased risk for atherosclerotic cardiovascular disease by virtue of his low HDL cholesterol, high triglycerides, and diabetes,[21] factors that would predispose to coronary atherosclerotic plaques. However, by coronary angiography, the widely patent, smooth-walled right, left main, and left anterior descending coronary arteries showed no evidence of occlusive atherosclerotic plaque. The patient's heritable hypofibrinolytic and prothrombotic traits apparently promoted thrombus formation and retention in the totally occluded distal aspect of the second obtuse marginal branch of the circumflex coronary artery. The patient did not have homozygosity or heterozygosity for the $P1^{A2}$ polymorphism of the glycoprotein IIIa gene, previously shown to be associated with premature coronary artery disease.[14]

Homozygosity for the thrombophilic MTHFR defect is common, found in 15% of patients with cardiovascular disease and in approximately 5% of healthy normal controls.[9]

Homozygosity (4G/4G) and heterozygosity (4G/5G) for the PAI-1 promotor genotype are very common, found in 43% and 41% of patients with a first myocardial infarction before age 45 and in 26% and 54% of healthy normal controls.[5] The prevalence of the 4G allele is significantly higher in patients with myocardial infarction before age 45 than in controls (allele frequencies, 0.63 *v* 0.53).[5]

Heterozygosity for the point mutation in the gene coding for coagulation factor V is common, found in 11.6% of those with venous thrombosis and/or pulmonary embolism and in 6% of men without vascular disease.[10]

Assuming that the MTHFR homozygosity (15% likelihood[9]; chromosome 1), 4G/5G heterozygosity (41% likelihood[5]; chromosome 7), and mutant factor V Leiden heterozygosity (11.6% likelihood[10]; chromosome 1) were not linked heritable defects, the likelihood of their concurrent appearance in a single patient with premature myocardial infarction would be estimated to be 0.7% (15% × 41% × 11.6%), or one per 143 patients.

In patients with severe premature coronary artery disease, we suggest that interactions between prothrombotic factors, hypofibrinolysis, and hyperlipidemia-atherosclerosis be regularly evalu-

ated, since such interactions may have ramifications for the outcome of short- and long-term secondary prevention. We speculate that coronary artery balloon angioplasty, atherectomy, or stent placement may fail with thrombotic reocclusion of arteries in patients with heritable prothrombotic factors and/or hypofibrinolysis. Patients with prothrombotic factors and/or hypofibrinolysis and premature myocardial infarction might also be candidates for anticoagulation. Moreover, in patients with heritable prothrombotic factors or hypofibrinolysis, it should be important to optimize lipid and lipoprotein cholesterol[21] levels with the goal of stabilizing coronary plaques to reduce the likelihood of rupture and thrombosis.[23]

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