Myocardial Infarction and 5,10-Methylenetetrahydro folate Reductase Gene Mutation

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A 40-year-old woman with previous venous thrombosis in the lower limbs had recurrent myocardial infarction in the early puerperium. The only documented risk factor was an elevated level of plasma homocysteine, associated to a heterozygotic anomaly in the enzyme responsible for its metabolism, 5,10-methylenetetrahydrofolate reductase. The case and approaches to treatment are discussed.

Key words: *Myocardial infarction. Thrombosis. Gene mutation. Hyperhomocysteinemia.*

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Infarto de miocardio y mutación de la enzima 5,10-metilentetrahidrofolato reductasa

Paciente de 40 años de edad con antecedentes de trombosis venosa de miembros inferiores que en el puerperio precoz presentó un infarto agudo de miocardio recurrente. El único factor de riesgo documentado fue un valor elevado de homocisteína plasmática, asociado con una anomalía heterocigótica de la enzima 5,10-metilentetrahidrofolato reductasa, encargada de su metabolismo. Se discute el caso y las posibilidades terapéuticas.

Palabras clave: *Infarto de miocardio. Trombosis. Mutación génica. Hiperhomocisteinemia.*

INTRODUCTION

In 1969, McCully[1] reported autopsy findings of thrombosis and atherosclerosis in two children with hyperhomocysteinemia and, for the first time, demonstrated that there may be a relationship between raised plasma homocysteine concentrations and vascular disease. Subsequent studies have confirmed this hypothesized relationship and have established that this biochemical abnormality is an independent risk factor for atherosclerosis and atherothrombosis.[2]

Homocysteine is a sulfurated amino acid that is formed during methionine metabolism. Elevated plasma levels of the compound result either from genetic defects in the enzymes involved in this process or from nutritional deficiencies in essential vitamin cofactors, such as vitamin B_6, vitamin B_{12}, and folic acid.

This report concerns the case of a patient who experienced recurrent acute myocardial infarction 11 days after giving birth by cesarean section. She had a history of venous thrombosis in the lower limbs. Her only cardiovascular risk factor was an elevated plasma homocysteine level that was associated with a heterozygous defect in the gene for the enzyme 5,10-methylenetetrahydrofolate reductase, which is involved in homocysteine metabolism.

CASE REPORT

A 40-year-old patient was admitted to the intensive care unit with an acute anteroseptal myocardial infarction and an elevated ST segment some 20 hours after first experiencing pain. Eleven days previously, she had undergone a cesarean section for a second pregnancy that had been carried to term. Her only relevant medical history was a number of previous episodes of thrombophlebitis in the lower limbs.

On her arrival at the intensive care unit, urgent catheterization was indicated because of the presence of persistent chest pain. Anterolateral and apical hypokinesia were noted in the left ventricle and there was a depressed left ventricular ejection fraction of 48%. Severe proximal and medial stenosis of the

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ABREVIATIONS

AMI: acute myocardial infarction.
LV: left ventricle.
LVEF: left ventricular ejection fraction.

anterior interventricular branch of the left coronary artery, due largely to thrombosis, was observed. There were no other associated lesions. Arterial flow was re-established throughout the vessel by predilatation and stent implantation. This procedure resulted in a residual flow of TIMI (thrombolysis in myocardial infarction) grade 3 (Figure 1).

Six hours after the procedure, a new episode of prolonged angina occurred. This episode was not accompanied by significant electrocardiographic or enzymatic changes and was not diminished by intravenous nitroglycerin or morphine administration. Exploratory catheterization was carried out. A new thrombotic stenosis had occurred in the medial segment of the second anterior interventricular septal artery. The vessel was reopened by balloon angioplasty, while the anterior interventricular branch of the left coronary artery remained patent.

On the fourth day, anginal chest pain recurred, there was inferior ST segment elevation accompanied by a transitory second-degree atrioventricular block, and cardiac enzyme levels were elevated. These observations were compatible with acute inferior myocardial infarction. Catheterization was again carried out and showed proximal thrombotic occlusion of the right coronary artery. The vessel lumen was reopened by dilatation and the sequential placement of two stents in proximal and medial segments (Figure 2). Similarly, the significant proximal thrombotic stenoses observed in the anterior interventricular branch of the left coronary artery and in the second anterior interventricular septal artery were treated by direct stent implantation.

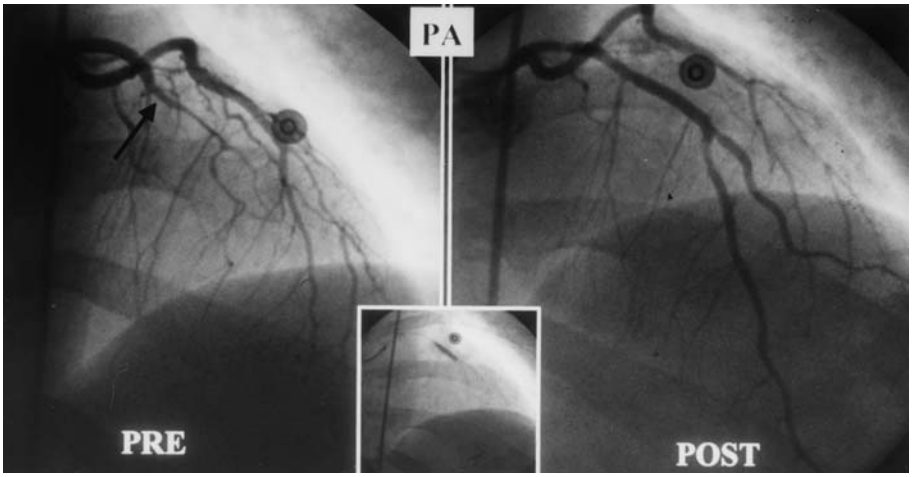

Fig. 1. Dilatation of the proximal anterior interventricular branch of the left coronary artery followed by the implantation of two stents.

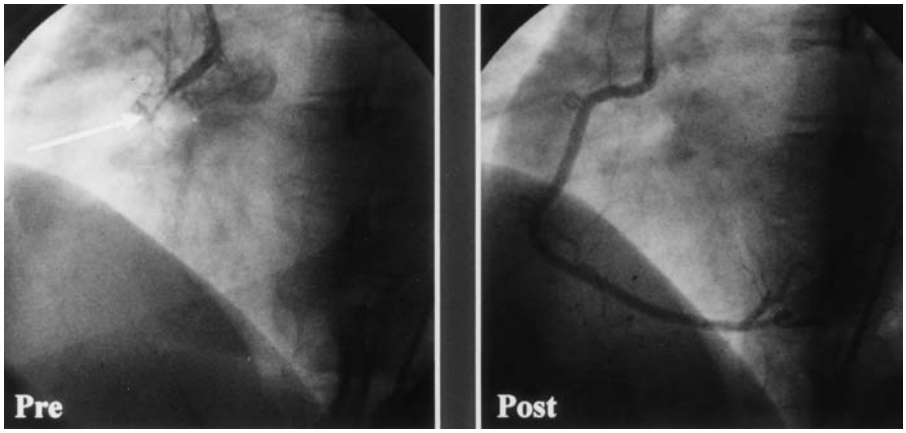

Fig. 2. Revascularization of the right coronary artery by direct stent implantation in two locations.

The levels of platelets, fibrinogen, prothrombin, protein S, protein C, antithrombin III, and factor V Leiden were all found to be normal. Tests for anti-*Chlamydia pneumoniae*, and antinuclear and anticardiolipin antibodies gave negative results. A complete genotype analysis for cardiovascular risk factors was carried out on total DNA extracted from blood. This showed a heterozygous defect in the 5,10-methylenetetrahydrofolate reductase gene, which had several mutations. This observation was associated with an elevated plasma homocysteine level of 30 mol/L. Oral vitamin B_6, vitamin B_{12} and folic acid supplementation was started. The patient´s subsequent clinical course up until discharge and during the following 6 months was satisfactory, and no new episodes of cardiac ischemia occurred. The plasma homocysteine level normalized 3 months after starting vitamin supplementation.

DISCUSSION

The occurrence of ischemic heart disease during pregnancy or the puerperium is uncommon. In our patient, the only cardiovascular risk factors were the probable prothrombotic state associated with her recent pregnancy and a moderate increase in plasma homocysteine level resulting from the mutations observed in the 5,10-methylenetetrahydrofolate reductase gene.

Homocysteine is a sulfurated amino acid that is formed during the metabolism of methionine, an essential amino acid derived from dietary proteins. Typically, hyperhomocysteinemia is the result of genetic defects in the enzyme 5,10-methylenetetrahydrofolate reductase. This enzyme facilitates the reconversion of homocysteine to methionine by means of remethylation. Less frequently, hyperhomocysteinemia is due to nutritional deficiencies in essential vitamin cofactors, such as vitamin B_6, vitamin B_{12}, and folic acid.

Numerous studies have indicated that an increased plasma homocysteine level is a risk factor for occlusive arterial or venous disease.[2-4] One Spanish study carried out in 202 patients with coronary disease[5] showed that 26% had hyperhomocysteinemia. However, another investigation in Puerto Rico[6] showed that the level of hyperhomocysteinemia was not a reliable indicator of the severity of the observed coronary lesions.

Affected patients are usually asymptomatic until the third or fourth decade of life, when they prematurely develop coronary artery disease as well as recurrent thrombosis of the arterial and venous systems, which could explain our patient´s history of repeated thrombophlebitis of the lower limbs.

Experimental evidence suggests that the atherogenic tendency associated with hyperhomocysteinemia is caused by endothelial dysfunction and abnormal platelet function.[7,8] Administration of the vitamin cofactors mentioned above can normalize the homocysteine concentration, usually within 4-6 weeks from the initiation of therapy, as occurred in our patient. However, currently, the impact on cardiovascular morbidity and mortality is unknown. These uncertainties mean that, at present, routine measurement of the plasma homocysteine concentration cannot be recommended, except in patients who have premature atherosclerosis that cannot be explained by the presence of known cardiovascular risk factors, as was the case in our patient. This subgroup of patients could benefit from long-term supplementation with the vitamin cofactors mentioned above.

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