

CASE REPORT

MYOCARDIAL INFARCTION IN A YOUNG PATIENT WITH METHYLENE TETRAHYDROFOLATE REDUCTASE (MTHFR) GENE MUTATION

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We report a case of a 40 year old female patient who presents with chest pain and is diagnosed with a inferior myocardial infarction (MI) and when tested she was found to be heterozygous (C677T) for Methylene Tetrahydrofolate Reductase (MTHFR) gene mutation. The patient was stopped from using the OCP and was started on life-long oral daily folic acid supplementation. Screening of her siblings led to the discovery that her two sisters were both homozygous for MTHFR deficiency. This case clearly illustrates that we as clinicians must look beyond the box and not just treat common conditions like CHD. When the risk factors do not add up, we must go in search of an identifiable cause that can have future benefit for the patient and other family members.

Keywords: Methylene Tetrahydrofolate Reductase gene mutation, Myocardial Infarction, Hyperhomocysteinaemia, Oral Contraceptive Pill, Gene Polymorphisms

INTRODUCTION

Modifiable risk factors for CHD include high blood pressure, high blood cholesterol, smoking, obesity, physical inactivity, diabetes, and stress. When a patient presents with the typical features of CHD (like ours) but do not have the modifiable risk factors, genetic causes should be considered. A limited number of genetic variants are proven to be independent risk factors for thromboembolism. These include mutations in the genes encoding the natural anticoagulants antithrombin, protein C and protein S, and the clotting factors fibrinogen, prothrombin and factor V. A common genetic variant in the MTHFR gene involving a cytosine to thymidine (C-->T) transition at nucleotide 677 is associated with reduced enzyme activity, altered folate status and potentially higher folate requirements (1). We report a case of a 40 year old female patient who presents with chest pain and is diagnosed with a inferior myocardial infarction (MI) and when tested she was found to be heterozygous (C677T) for Methylene Tetrahydrofolate Reductase (MTHFR) gene mutation.

CASE

A 40 year old previously well female presented to the Accident and Emergency Department (AED) with a one-hour history of central chest pain. The pain came on at rest and radiated down her left arm and it was associated with nausea and sweating, but no syncope. She had no associated shortness of breath or palpitations. She attended the AED where she was given sub-lingual nitrates which failed to relieve her chest pain.

Of note, she had no past medical history of diabetes, hypertension, coronary heart disease (CHD) or peptic ulcer disease. However, she was currently taking the combined oral contraceptive pill (OCP). She had no relevant family history and had always been a non-smoker.

Examination revealed a young female in moderate distress with a blood pressure of 119/66 mmHg, regular pulse rate of 92 beats/minute and a respiratory rate 12/minute with oxygen saturation of 98% on air. Physical examination was normal. An electrocardiogram (ECG) was performed on arrival in the AED which showed ST segment elevation in leads II, III and aVF, which persisted with repeated ECGs. Because of the typical chest pain and the associated ECG changes, the patient was diagnosed as having an inferior myocardial infarction (MI) and was thrombolysed with Tenecteplase intravenously followed by intravenous heparin.

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An echocardiogram revealed mildly reduced left ventricular function and apico-septal hypokinesia with a mildly hypokinetic left ventricle but no left ventricular thrombus. Heart valves appeared structurally normal. Blood tests revealed normal full blood count, cholesterol (including total and LDL: HDL ratio), triglycerides, renal, liver function, folate levels and vitamin B12 levels but an elevated Troponin I of 14.7 and an elevated plasma homocysteine level of 75 $\mu\text{mol/L}$. This plasma homocysteine level was repeated after a 12 hour fast and was still elevated at 63 $\mu\text{mol/L}$.

The patient remained pain-free post-thrombolysis and the ECG showed gradual improvement with reversion of the ST segments to the baseline. The patient spent seven days in hospital during which time she made an uneventful recovery. She was referred for a coronary angiogram, which revealed normal left ventricular function, and coronary artery anatomy appeared normal.

In view of her young age and lack of risk factors, the possibility of an inheritable thrombophilia was considered and a prothrombotic screen was done after patient was taken off Heparin. This revealed normal levels of factor VIII, IX, anti-thrombin, activated protein C resistance ratio, protein C and S, negative for lupus anticoagulant, prothrombin gene mutation, cystathionine B-synthase mutation and factor V Leiden DNA analysis. However, it was noted that she was heterozygous (C677T) for Methylene Tetrahydrofolate Reductase (MTHFR) gene mutation.

Haematological advice suggested that life-long Warfarin was unwarranted. Her homocysteine, folate and vitamin B12 status was determined and her homocysteine levels were found to be persistently elevated (42-66 $\mu\text{mol/L}$). Thus she was withdrawn from the OCP and started on life-long folic acid supplementation. The patient has been followed up as an outpatient at regular intervals (initially six weekly and now three monthly) and has remained quite well having no further events.

She had informed her siblings of her condition and they opted for genetic testing. The results showed that both her sisters were homozygous for MTHFR gene mutation, though they have remained asymptomatic.

DISCUSSION

Modifiable risk factors for CHD include high blood pressure, high blood cholesterol,

smoking, obesity, physical inactivity, diabetes, and stress. Other factors, such as gender, genetics, and age are not controllable. When a patient presents with the typical features of CHD (like ours) but do not have the modifiable risk factors, genetic causes should be considered.

A limited number of genetic variants are proven to be independent risk factors for thromboembolism. These include mutations in the genes encoding the natural anticoagulants antithrombin, protein C and protein S, and the clotting factors fibrinogen, prothrombin and factor V.

A common genetic variant in the MTHFR gene involving a cytosine to thymidine (C-->T) transition at nucleotide 677 is associated with reduced enzyme activity, altered folate status and potentially higher folate requirements. The C677T mutation of the MTHFR gene leads to C/C, C/T and T/T genotypes, which increase the plasma homocysteine concentration in humans. Hyperhomocysteinemia is associated with premature atherosclerosis and venous thromboembolism.

The lesions of coronary atherosclerosis represent the result of a complex, multi-cellular, inflammatory-healing response in the coronary arterial wall. Many cellular and molecular studies have suggested a role for tissue homocysteine in endothelial cell injury. Gene polymorphisms in relation with numerous risk factors might increase the incidence of CHD (1).

In terms of treatment options, hyperhomocysteinemia because of the C677T MTHFR allele may be corrected with oral folic acid therapy (2). Vitamin supplementation reduced homocysteine levels dependent on the MTHFR genotype (36% TT, 25% CT, 22% CC) but did have an effect in all genotypes (3). In venous and arterial thrombosis cases, MTHFR and homocysteine data led to effective dietary supplementation with a reduced risk of disease progression and this has been noted in our patient as well.

Genetic abnormalities specific to factor V, prothrombin and homocysteine metabolism increase the risk for myocardial infarction and ischemic stroke, particularly among younger patients and women. Because the overall association is only modest, screening studies should be limited to carefully selected patient populations. The individual propensity for arterial and venous thrombosis is likely to be influenced by differing local mechanisms, systemic mechanisms, or both (4). This highlights different aspects of our

case report. Firstly, screening in our patient was merely undertaken because of her lack of risk factors and her young age. Also, it is thought that in this particular case, her being on the OCP acted as a confounding factor, since on its own the relative risk of a thromboembolic event is quite small. A literature search only found two similar reports of an association of MTHFR gene mutation. The first (5) was published in 1997 and described 35 year-old male who also suffered a recent MI. He was found to be homozygous for the mutation in the methyl enetetrahydrofolate reductase (MTHFR) gene causing homocysteinemia, and heterozygous for the mutant factor V Leiden gene causing resistance to activated protein C. He was also found to have other major risk factors for coronary artery disease including previously undiagnosed adult-onset diabetes, high triglycerides and low high-density lipoprotein (HDL) cholesterol. The second (6) published in 2003 was of a 32 year-old Hungarian male smoker who had an anterolateral MI and was later found to be homozygous for MTHFR gene mutation as well as having antiphospholipid antibody syndrome.

Discussion of prognosis and prediction of further events in patients with this gene mutation is quite difficult. Given the heterogeneity of mutations, no one seems to be able to predict neurological and/or vascular symptoms (7). However, we as clinicians must look beyond the box and not just treat common conditions like CHD. When the risk factors do not add up, we must go in search of an identifiable cause that can have future benefit for the patient and other family members.

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