Brachial artery aneurysm accompanying a homozygous methylenetetrahydrofolate reductase mutation

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Abstract

Elevated plasma homocysteine (Hcy) is one of the suggested risk factors for endothelial dysfunction. There is evidence of association between raised plasma Hcy and an increased risk of developing peripheral arterial disease. A causal relationship, however, has not been established. In this report, a 37-year old male patient with the complaints of intermittent hand pain is presented. Brachial artery aneurysm accompanying a homozygous methylenetetrahydrofolate reductase mutation was detected.

Keyword: Brachial artery aneurysm

INTRODUCTION

Methylenetetrahydrofolate reductase (MTHFR) irreversibly reduces 5,10-methylenetetrahydrofolate (substrate) to 5-methyltetrahydrofolate (product). MTHFR is a key enzyme that has a role in purine–pyrimidine synthesis, in methylation reactions and in folate metabolism in which homocysteine (Hcy) is converted to methionine. MTHFR gene, which is responsible for MTHFR enzyme synthesis, is located on the short (p) arm of chromosome 1 at position 36.3 (1p36.3) and consists of 11 exons. The MTHFR nucleotide at position 677 in the gene has two possibilities: C (cytosine) or T (thymine). The normal allele is C at position 677, and the 677T allele encodes the thermolabile enzyme with reduced activity.

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CASE REPORT

A 37-year old male patient with complaints of intermittent hand pain was admitted to our cardiovascular surgery department with hand ischaemia. On physical examination, pulses of ulnar and radial arteries were not palpable; however, a mass was palpated in the middle ventral border of the right arm. The patient did not have history of trauma, hypercholesterolemia, smoking, infection and hypertension. The Doppler examination of the right upper extremity revealed a right brachial artery aneurysm about 35 × 20 mm in size. Doppler examination in other parts of the arterial tree was completely normal. Initial laboratory evaluation indicated hypochromic, microcytic anaemia with a haemoglobin level of 9.6 g/dl, haematocrit level of 29%, mean corpuscular volume of 74.6 fl, mean corpuscular haemoglobin of 24.6 pg, platelet count of 431 k/l and white blood cell count of 8.9 k/l. Serum ferritin values were low (3 ng/ml). Prothrombin time, activated partial thromboplastin time, factors II, V, VII, VIII, X, plasminogen activity and antigen, protein C, protein S, antithrombin III and haemoglobin electrophoresis were within normal limits. Both Factor V Leiden and prothrombin gene 20210A mutations were negative. There were no abnormal findings in rheumatological examination. However, the only abnormality found was hyperhomocysteinaemia (38.3 mmol/l) in association with a homozygous MTHFR mutation.

The patient was operated on under general anaesthesia. Intraoperatively, a saccular aneurysm was determined; proximal and distal ends of brachial artery were looped (Fig. 1A). The aneurysmal sac of the brachial artery was opened with scissors. Thrombus material within the lumen was removed. Finally, the artery was repaired with saphenous vein interposition in a usual manner (Fig. 1B). Following operation, the pulses of ulnar and radial arteries were palpable in the right forearm. Histological examination revealed structural deterioration of the vessel wall. This included fibrotic changes and thickening of the intima with mild atheromatous lesions, thinning of the media with the replacement of smooth muscle cells by fibrosis, a disrupted internal elastic membrane and numerous microthrombi adherent to the intima.

The whole postoperative course was uneventful, and the patient was discharged on the third postoperative day.

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DISCUSSION

Hyperhomocysteinaemia is an independent risk factor for the early development of atherosclerosis and a risk factor for thromboembolic venous or arterial disease [1]. Homocystinuria due to severe cystathionine beta-synthase or 5,10-MTHFR deficiency is associated with severe hyperhomocysteinaemia and is characterized by atherosclerosis and thromboembolic disease [1]. Khandanpour et al. [1] reported the analysis of the genotypes of 1432 patients with peripheral arterial disease and 2405 controls in a case-control study and meta-analysis. Although the precise mechanisms of Hcy-induced vascular injury remain poorly understood, they found that the MTHFR C677T allele increased the risk of peripheral arterial disease in homozygotes (TT genotype) with an odds ratio of 1.99 (95% confidence interval 1.09–3.63). In another study, Xu et al. [2] demonstrated that methionine diet-induced hyperhomocysteinaemia accelerates cerebral aneurysm formation in an experimental rat model. They also observed increased expression of matrix metalloproteinase-2 and -9 (MMP-2 and -9) in aneurysm of arterial walls. The study by Takagi et al. [3] suggested that circulating MMP-9 concentrations were higher in patients with abdominal aortic aneurysm, and Cacoub et al. [4] reported 2 male patients with the age of 32 and 38 of isolated aneurysm of both popliteal arteries and the right cubital artery in association with MTHFR mutation and hyperhomocysteinaemia, respectively. Mohan et al. [5] reported a 64-year old man with hyperhomocysteinaemia in association with MTHFR mutation and an isolated left external iliac artery aneurysm.

Hyperhomocysteinaemia is reported to cause endothelial dysfunction/injury [1]. It primarily acts through oxidative inactivation of endothelium-derived nitric oxide, a major mediator of vascular relaxation and increases the rate of endothelial senescence.

Hcy is metabolized by one of two divergent pathways: trans-sulphuration and remethylation. The trans-sulphuration of Hcy to cysteine is catalyzed by cystathionine-β-synthase, a process that requires pyridoxal phosphate (vitamin B6) as a cofactor.

Remethylation of Hcy produces methionine. This reaction is catalyzed either by methionine synthase or by betaine-Hcy methyltransferase and requires methyl donor as a substrate that is met by methyl THF with the reduction of 5,10-methylene THF. The reduction of 5,10-methylene THF requires vitamin B2 (riboflavin) as a cofactor. In addition, the enzyme methionine synthase requires methylcobalamin as a cofactor, which is produced from the methylation of vitamin B12 (cobalamin). Therefore, the vitamin supplements have been suggested for lowering the serum Hcy levels and decreasing hyperhomocysteinaemia-related complications and clinical manifestations, including cardiovascular diseases, stroke, atherosclerosis, occlusive and aneurysmal vascular diseases.

The patient described in this report was very young, and hyperhomocysteinaemia was the only abnormality detected by exhaustive laboratory testing. This may suggest that the relationship between aneurysm formation with thromboembolic events, and hyperhomocysteinaemia was not coincidental. However, a large series of studies should be performed to demonstrate the relation of MTHR mutation with arterial aneurysm formation.

Conflict of interest: none declared.

REFERENCES