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Case report / Olgu Sunumu

Methylenetetrahydrofolate reductase polymorphism in a case with atrial septal defect, deep venous thrombosis, thromboembolism and recurrent spontaneous abortion

Atriyal septal defekt, derin ven trombozu, tromboembolizm ve tekrarlayan spontan abortusu olan bir olguda metilentetrahidrofolat redüktaz polimorfizmi

Adem Güler,[1] Mehmet Ali Şahin,[1] Murat Tavlaşoğlu,[1] Mehmet Yokuşoğlu[2]

[1]Department of Cardiovascular Surgery, Gülhane Military Medical School, Ankara, Turkey;
[2]Department of Cardiology, Gülhane Military Medical School, Ankara, Turkey

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the folate metabolism, where homocysteine converted to methionine. Methylenetetrahydrofolate reductase gene polymorphism is responsible for hyperhomocysteinemia resulting congenital heart defects, hypercoagulable states and recurrent abortion. A 30-year-old female was referred to our department with the diagnosis of atrial septal defect. In her medical history, she had two pregnancies with spontaneous abortus, deep venous thrombosis attacks, pulmonary thromboembolism and paradoxical cerebral embolus. The genetic work-up revealed heterozygote MTHFR C677T mutation. We recommend suspecting MTHFR polymorphism in young fertile women with a history of spontaneous abortus or deep venous thrombosis or congenital heart disease with a paradoxical cerebral embolus.

Key words: Atrial septal defect; deep venous thrombosis; methylenetetrahydrofolate reductase; spontaneous abortion; thromboembolism.

Metilentetrahidrofolat redüktaz (MTHFR), homosisteini metionine dönüştüren folat metabolizmasında temel enzimdir. Metilentetrahidrofolat redüktaz gen polimorfizmi hiperhosisteinemiden sorumlu olup, doğuştan kalp defektleri, hiperkoagülasyon ve tekrarlayan abortuslara neden olur. Otuz yaşındaki kadın hasta atriyal septal defekt tanısıyla kliniğimize yönlendirildi. Hastanın tıbbi öyküsünde spontan abortus ile sonuçlanan iki gebeliği, derin venöz tromboz atakları, pulmoner emboli ve paradoks serebral emboli vardı. Genetik çalışma sonucunda heterozigot MTHFR C677T mutayonu saptandı. Spontan abortus veya derin ven trombozu veya paradoks serebral emboli ile birlikte doğuştan kalp hastalığı olan genç doğurgan kadın hastalarda MTHFR polimorfizminden şüphelenmeyi önermekteyiz.

Anahtar sözcükler: Atriyal septal defekt; derin ven trombozu; metilentetrahidrofolat redüktaz; spontan abortus; tromboembolizm.

Methylenetetrahydrofolate reductase (MTHFR) irreversibly reduces 5,10-methylenetetrahydrofolate (substrate) to 5-methyltetrahydrofolate (product).[1] The MTHFR is a key enzyme that has a role in purin-pyrimidine synthesis, in methylation reactions, and in folate metabolism in which homocysteine is converted to methionine.[2] The 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 exones.

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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Correspondence: Mehmet Yokuşoğlu, M.D. Gülhane Askeri Tıp Akademisi Kardiyoloji Anabilim Dalı, 06010 Etlik, Ankara, Turkey.
Tel: +90 312 - 304 42 67 e-mail: myokusoglu@yahoo.com

Individuals with two copies of 677C (677CC) have the normal or wild-type genotype. Mild MTHFR deficiency is said to be found in 677TT individuals (homozygous), and these individuals (heterozygotes) are almost the same as those who are normal because the normal MTHFR can make up for the thermolabile version, so the degree of enzyme thermolability (assessed as residual activity after heat inactivation) is much greater in 677TT individuals (18-22%) compared with those that are 677CT (56%) and 677CC (66-67%).[3] Individuals with 677TT are predisposed to mild hyperhomocysteinemia because they have less active MTHFR available to produce 5-methyltetrahydrofolate (which is used to decrease homocysteine). A low dietary intake of folate can also cause mild hyperhomocysteinemia.

In addition, in another study, not only were high serum homocysteine levels and an increased risk of congenital heart disease observed in these patients, but increased coagulation tendency and an increased risk of paradoxical cerebral embolism were seen as well.[3]

CASE REPORT

A 30-year-old female was referred to our department with the diagnosis of atrial septal defect (ASD). Her medical history revealed two pregnancies with spontaneous abortus, and her third pregnancy resulted in a healthy newborn that was delivered on time. She also had deep venous thrombosis (DVT) attacks that were diagnosed with Doppler ultrasonography, pulmonary thromboembolism (PTE) that was diagnosed with pulmonary artery computed tomography (CT) before her pregnancies, and paradoxical cerebral embolus (PCE) that was diagnosed in the neurology department of another medical center. On her physical and laboratory examinations, there were no signs of sequelae of DVT, PTE, or carotid thromboendarterectomy (CTE). Also, no abnormality was detected in the patient's preoperative whole blood count and clotting profile (white blood count: 4.900/µl, platelet count: 292.000/µl, red blood count: 4.520.000/µl, hemoglobin: 12.6 g/dl, activated PTT: 44.6 seconds, prothrombin time: 15.4 seconds and international normalized ratio: 1.07). Her normal plasma homocysteine and folate levels were also determined.

Based on her medical history and her congenital heart defect, we suspected a genetic disorder and focused on the MTHFR gene polymorphism even though her plasma homocysteine and folate levels were within the normal range. The genetic work-up revealed a heterozygote MTHFR C677T mutation.

After this, the patient had surgery and a secundum-type ASD was repaired with primary stitches. Her postoperative course was uneventful. Low-molecular-weight heparin was administered in the first five postoperative days, and warfarin was added on the fourth postoperative day. She was discharged on the postoperative sixth day with oral medications of folic acid 5 mg 1x1, pyridoxine 50 mg 1x1, and warfarin.

DISCUSSION

Although it is still controversial, associations, such as ASD, pulmonary artery stenosis, and aortic coarctation, have been determined between the MTHFR polymorphism and congenital heart disease. These especially occur in patients having the C677TT genotype.[5] In addition, polymorphism of the MTHFR gene has been shown to be a maternal risk factor for Down syndrome and congenital heart defects.[6] Although, the prevalence of congenital heart defects varies between 0.7-1% in live- born children, there is a much higher percentage in those aborted spontaneously or those that are stillborn.[7] The two spontaneous abortions in our case can be explained by the fact that increased rates of miscarriage have been noted with the presence of the maternal MTHFR polymorphism, which causes heart defects.[8] In order to prevent these defects in patients with the MTHFR polymorphism, supplemental folate is advised and has been found to be effective.[9]

According to recent studies, having the MTHFR gene polymorphism not only poses a risk for paradoxical cerebral thromboembolism, but it also may be a sign of a congenital heart defect. Additonally, it has also been determined that the MTHFR C677TT genotype is a risk factor for cardiovascular events.[10]

In conclusion, we recommend suspicion of the MTHFR polymorphism in a young fertile female with a history of spontaneous abortions, DVT, or congenital heart disease with a paradoxical cerebral embolus even if normal plasma homocysteine levels are present.

Declaration of conflicting interests

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REFERENCES

1. Schwahn B, Rozen R. Polymorphisms in the methylenetetrahydrofolate reductase gene: clinical consequences. Am J Pharmacogenomics 2001;1:189-201.

2. Ma J, Stampfer MJ, Giovannucci E, Artigas C, Hunter DJ, Fuchs C, et al. Methylenetetrahydrofolate reductase polymorphism, dietary interactions, and risk of colorectal cancer. Cancer Res 1997;57:1098-102.
3. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995;10:111-3.
4. Palmieri V, Tufano A, Carmen Bonito M, Martino S, Sabatella M, Di Minno G, et al. Right-to-left shunt, atrial septal aneurysm and thrombophilia in patients with cryptogenic stroke or TIA vs. those with venous thrombo-embolism. Int J Cardiol 2008;130:99-102.
5. Wenstrom KD, Johanning GL, Johnston KE, DuBard M. Association of the C677T methylenetetrahydrofolate reductase mutation and elevated homocysteine levels with congenital cardiac malformations. Am J Obstet Gynecol 2001;184:806-12.
6. Brandalize AP, Bandinelli E, dos Santos PA, Roisenberg I, Schüler-Faccini L. Evaluation of C677T and A1298C polymorphisms of the MTHFR gene as maternal risk factors for Down syndrome and congenital heart defects. Am J Med Genet A 2009;149A:2080-7.
7. Grech V, Gatt M. Syndromes and malformations associated with congenital heart disease in a population-based study. Int J Cardiol 1999;68:151-6.
8. George L, Mills JL, Johansson AL, Nordmark A, Olander B, Granath F, et al. Plasma folate levels and risk of spontaneous abortion. JAMA 2002;288:1867-73.
9. Junker R, Kotthoff S, Vielhaber H, Halimeh S, Kosch A, Koch HG, et al. Infant methylenetetrahydrofolate reductase 677TT genotype is a risk factor for congenital heart disease. Cardiovasc Res 2001;51:251-4.
10. Ibrahim S, El Dessokiy O. Prevalence of methylenetetrahydrofolate gene (MTHFR) C677T polymorphism among chronic hemodialysis patients and its association with cardiovascular disease: a cross-sectional analysis. Clin Exp Nephrol 2009;13:501-7.