CASE REPORT

PREDISPOSING ROLE OF HETEROZYGOTE MTHFR A1298C MUTATION IN VENOUS THROMBOSIS IN A PREGNANT PATIENT: A CASE REPORT

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ABSTRACT
Congenital and acquired thrombophilia are associated with an increased risk of pregnancy-associated venous thrombosis (VT). Several genetic mechanisms have been investigated for their possible relationship with VT. Methyl tetrahydrofolate reductase gene polymorphisms are frequently in the MTHFR gene, which leads to a C to T change at position 677, has been suggested to alter the thrombohemostasis process and thrombophilia. Also, it has been found that MTHFR C1298C or MTHFR A1298C have no effect on the risk of VT. Herein, we describe deep VT (DVT) secondary to heterozygous MTHFR A1298C mutation in pregnant woman.

KEY-WORDS: Pregnancy; MTHFR A1298C Mutation; Venous Thrombosis

Introduction

Congenital and acquired thrombophilia are associated with an increased risk of pregnancy-associated venous thrombosis (VT) and foetal loss. Several genetic mechanisms have been investigated for their possible relationship with VT. Methyl tetrahydrofolate reductase (MTHFR) plays a key role in folate metabolism by channelling one-carbon units between nucleotide synthesis and methylation reactions.[1] This enzyme deficiency leads to hyperhomo-cysteinemia and homocystinuria, with altered folate distribution and a phenotype that is characterized by damage to the vascular system.[1] Similar to the other gene, MTHFR gene has its polymorphisms. A frequent polymorphism in the MTHFR gene, which leads to a C to T change at position 677, has been suggested to alter the thrombohemostasis process and thrombophilia.[1] Also, it has been found that MTHFR C1298C or MTHFR A1298C have no effect on the risk of VT.[1]

Herein, we describe deep venous thrombosis secondary to heterozygous MTHFR A1298C mutation in pregnant woman.

Case Report

Written informed consent was obtained from the patient. A 32-years-old woman, who has been pregnant for 16 weeks, admitted to our outpatient clinic for routine thyroid function test control. She was also complaining of left leg pain, swelling and warmth for two days. On physical examination her left lower extremity was warmer and 2.5 cm larger than right lower extremity in circumference. The remainder of her examination yielded unremarkable findings. Because of the pregnancy, the lower extremity Doppler ultrasonography (US) was obtained based on the assumption that pre-diagnosis of the patient was acute deep vein thrombosis (DVT). It revealed a acute phase thrombus in the left common femoral vein. The patient diagnosed as DVT. For treatment, low-molecular-weight heparin (enoxaparin) was administered at 1 mg/kg subcutaneously twice daily.

She did not have a history of smoking, trauma, operation, cancer, hematologic diseases, vasculitis, venous insufficiency, thrombotic event. Complete blood count, renal and liver functions, urine

analysis were all normal. Further tests for etiology including homocysteine, vitamin B12, anti-nuclear antibody, rheumatoid factor, lupus anti-coagulant, anti-cardiolipin immunoglobulin M and G levels were negative. Among the genetic tests performed by using PCR Chain reaction-restriction fragment length polymorphism, Factor V Leiden, prothrombin G20210A, MTHFR C677T mutations were found to be negative. Only heterozygous MTHFR A1298C gene mutation was positive in patient.

Complaints of the patient were markedly reduced with in the first week of the treatment and no thrombosis was found in the lower extremity Doppler US performed for control.

Discussion

Deep vein thrombosis is an important cause of morbidity and mortality, which occurs as a result of venous stasis, hypercoagulopathy and vascular injury due to genetic and environmental factors.[2] As a result of MTHFR gene mutation, which is a reason for genetic thrombophilia, remethylation of the homocysteine into methionine is damaged; homocysteine levels, which result in arterial and venous thrombosis, increase.[3,4] Common mutation MTHFR C677T in homocysteine metabolism has been shown to cause increased homocysteine levels thus causing a predisposition to thrombosis. The other mutation in the same gene, in common polymorphism, A1298C, which changes a glutamate into an alanine; enzyme activity decreases, but, in general, homocysteine levels are not affected.[5] It is suggested that the decrease in this enzyme activity is associated with neural tube defects and can act in an additive manner in combination with C677T for thrombosis.[6] In India, it was also shown that DVT risk was increased by 3.5-fold when MTHFR 1298AC heterozygote mutation were combined with 677CT heterozygote mutation rather than the stand-alone MTHFR 1298AC heterozygote mutation.[7] Combination of A1298C and PAI-I heterozygote mutations was reported in a patient with renal vein thrombosis. In a previous study, it was found that, for MTHFR A1298C mutation, only double heterozygous or homozygous state could be a risk factor for thrombosis in Turkish society.[8]

Risk of venous thrombosis is increased by four-fold to five- fold in pregnancy. Deep venous thrombosis, which occurs during pregnancy, tends to be massive and located in proximal veins, for this reason it may progress to more serious complications.[9] Smoking, hypertension, diabetes, lupus, obesity, advanced age, thrombophilia and complications of pregnancy (such as increased hypercoagubility, increased venous capacitance and decreased venous outflow, mechanical obstruction by the gravid uterus, decreased mobility, multiple gestation) are responsible for increased risk of DVT in pregnancy.[10] Although pregnancy increases the risk of DVT, DVT does not occur in all pregnant women. In this study, we reported a pregnant patient, whose only risk factor for DVT was MTHFR A1298C heterozygote mutation. Thus, we showed that MTHFR A1298C heterozygote mutation was not that innocent, that the mutation may be associated with DVT, which could pave the way for significant maternal and foetal clinical situation in a common condition such as pregnancy as well as combination with other genetic mutations or homozygote mutation. Besides, we detected a normal homocysteine level in the patient with MTHFR A1298C mutation consistent with the previous data. This enzyme defect may lead to thrombosis by different mechanisms without resulting in hyperhomo-cysteinemia According to our opinion, our case at least shows that heterozygote MTHFR A1298C mutation will not be innocent as expected and that the mutation may result in development of thrombosis especially if there is a condition which creates a predisposition to thrombosis such as pregnancy. By taking into account the issues with regard to cost-effectiveness, relatives of the individuals with these gene mutations may be scanned in terms of MTHFR A1298C and other genetic thrombophilia factors and more intensive thrombosis prophylaxis or treatment methods may be considered when there are conditions such as pregnancy, trauma, and diseases, which increase the risk of thrombosis.

Conclusion

Herein, we describe DVT secondary to heterozygous MTHFR A1298C mutation in pregnant woman. Our case figure out that heterozygote MTHFR A1298C mutation will not be

innocent as expected and that the mutation may result in development of thrombosis especially if there is a condition which creates a predisposition to thrombosis such as pregnancy.

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