

Methyltetrahydrofolate Reductase Defect in Two Cases of Habitual Abortion: a Case Report

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Abstract

Background: Methyltetrahydrofolate reductase (MTHFR) defect is a result of a mutation in the encoding gene where thymidine is replaced by cytosine (C667T). Prevalence of the mutation varies in different societies. Resulting thermo labile MTHFR enzyme results in hyperhomocysteinemia which itself is a risk factor for thrombosis. Elevated plasma homocysteine levels also can result in neural tube defects, fetal death, abruption placenta and placental infarctions.

Case: We report two siblings presented with habitual abortus and were found to have heterozygote MTHFR defect.

Conclusion: We believe that even heterozygosis for MTHFR defect can cause spontaneous abortion alone or in combination with unknown factors. This accompanying unknown factor might be heterozygote β -fibrinogen-455 GA mutation that we found in both of our patients. Studies about this mutation reported especially high incidence of ischemic stroke in these patients. Further studies are needed to confirm whether MTHFR defect combined with β -fibrinogen-455 GA mutation definitely increase risk of spontaneous abortion. Folic acid supplementation and enoxaparin might be helpful, as in our patients, in the management of these patients.

Keywords: MTHFR defect, recurrent pregnancy loss, treatment.

Habituel abortus nedeniyle takip edilen iki olguda MTHFR defekti: Olgu sunumu

Amaç: Metiltetrahidrofolat redüktaz (MTHFR) enzimini kodlayan gende 677 nükleotid olan timidin yerine sitozin gelmesi ile ortaya çıkar (C677T). Mutasyonun sıklığı toplumlara göre farklılık göstermektedir. Bu mutasyon sonucunda oluşan termolabil MTHFR enzimi hiperhomosisteinemiye yol açmakta ve homosistein yüksekliği ise tromboz risk faktörü olarak belirtilmektedir. Kanda homosistein düzeyinin yükselmesi nöral tüp defekti, fetal kayıp, plasenta dekolmanı ve plasental infarkt riskini artırmaktadır.

Olgu: Bu çalışmada, kliniğimizde habituel abortusa neden olan heterozigot MTHFR defekti saptadığımız iki kardeş olgu sunulmuştur.

Sonuç: Tekrarlayan gebelik kayıplarının etiyolojisi ile ilgili olarak bugün için birçok mekanizma öne sürülmüş ve bu mekanizmalardan bazıları hala tam olarak açıklanamamıştır. Habituel abortusların nadir sebeplerinden biride MTHFR defektidir. Ancak literatürlerde farklı görüşlerin olması nedeniyle hala tesbit edilememiş başka anomalilerin, MTHFR defektiyle birlikte habituel abortusa neden olabileceği düşünülmektedir. Tedavide, bizim olgularımızda olduğu gibi, folik asit ve enoxaparin verilmesi, gebeliğin devamına olanak sağlayabilir.

Anahtar Sözcükler: MTHFR defekti, habituel abortus, tedavi.

Introduction

Habitual abortus is defined as spontaneous termination of two or more successive pregnancies before 20th weeks of pregnancy. Determinations of etiologic and prognostic factors are among the most difficult situations in obstetrics. About 15-33% of the recurrent abortus cases are idiopathic. Efficient utero-placental circulation, which can be effected from hemostasis disorders, is a prerequisite for continuation of a successful pregnancy. Thus, maternal thrombophilias (factor V Leiden mutation, MTHFR defect, Factor II mutations, protein C or S deficiencies) are also important disorders in obstetrics.¹

MTHFR is an essential enzyme for homocysteine metabolism. MTHFR and other gene mutations in homocysteine metabolism lead to hyperhomocysteinemia. In the MTHFR defect, mutation of C667T located in MTHFR gene results in replacement of alanine in the catalytic domain of MTHFR by valine. This change makes the enzyme thermo-labile. In turn, in vitro MTHFR activity decreases 70% and 35% in homozygote and heterozygote, respectively. On the other hand, plasma homocysteine levels in patients who are homozygous for C667T allele increase moderately and this is significant especially during folate deficiency periods. Heterozygous allele carrying patients have mildly increased levels plasma of homocysteine.^{2,3}

The exact mechanism between hyperhomocysteinemia and pregnancy loss is not known and several mechanisms like constitutional and neurologic effects on the fetus, increase in thrombogenic potential or thrombosis in the effected mother are proposed. MTHFR is a cause for hyperhomocysteinemia accompanying decreased folate levels which might cause mental retardation, skeletal abnormalities, premature vascular disease or thrombosis.

Hyperhomocysteinemia increases the risk of neural tube defect, fetal losses, abruptio placenta and placental infarction. Studies have shown borderline increases homozygous MTHFR defect in women with fetal losses and an increase in relative risk of fetal loss in women with this defect.⁴ It's still not clear whether folate supplementation decrease fetal loss risk.

MTHFR mutation is accepted as a risk factor in habitual abortus. Homozygote variant frequency have been reported to be elevated among women with three or more recurrent abortion in some studies while others couldn't find a relationship between fetal loss and MTHFR mutations, and still others reported similar or lower MTHFR mutation prevalence between idiopathic fetal losses and controls.^{5,8} We found MTHFR defect in two sisters leading to habitual abortus and decided to report this as there were conflicting data regarding MTHFR defect in the literature.

Case

The first case was a 30 y/o female who had 7 spontaneous abortions during the first trimester. Her sister, the second case, was 28 y/o woman who had 5 spontaneous abortions during the first trimester. The patients were consulted to our clinic for nonspecific complaints after being evaluated at the gynecology-obstetrics department of our university hospital. Both patients have normal physical examination findings including the vitals. Serum biochemistry, hormone levels and hemogram were unremarkable. Plasma homocysteine were measured as 15 $\mu\text{mol/l}$ (N: 5-12) in the first patient and 16 $\mu\text{mol/l}$ in the second. Heterozygote carrier state for MTHFR C667T and α -fibrinogen-455 G-A mutations were found in both patients. They didn't carry other thrombophilia producing defects like factor V G1691A, factor V H1299R, prothrombin G20210A, factor XIII

V34L, MTHFR A1298C, Apo B R3500Q, PAI-1, HPA¹, ACE or Apo E. Both of our patients received po folic acid 5 mg/d and sc enoxaparin 4000 IU/ 0.4 mL /day until 1 day before delivery. Both pregnancies carried on without adverse events leading to delivery of two healthy babies. Deliveries were with cesarean section; first patient's delivery was performed at the 36th week with a birth weight of 3.140 g. Second patient's delivery was performed at the 38th week with a birth weight of 2.980 g. patient's have not received heparin and advised to take low dose aspirin during nursery period. Oral anticoagulation was planned for the post-nursery period.

Discussion

Fetal loss is a frequent clinical entity. 15% of the pregnancies terminate with spontaneous abortion while 0.5-1% of the couples experience recurrent fetal losses. Habitual abortus is defined as spontaneous termination of two or more successive pregnancies before 20th weeks of pregnancy⁹ and is one of the most unknown areas in obstetrics. All fetal losses were in during the first trimester in both of our patients.

The most frequent cause of hereditary thrombophilias are factor V Leiden mutation and activated protein C resistance (APCR). Acquired or hereditary APCR have been proposed to be among the potential causes of placental circulatory failure. There are studies in the literature supporting a relationship between factor V Leiden and factor II G20210A mutations and recurrent fetal losses. These mutations are not only reported to be important risk factors for recurrent abortions but also for thrombosis, and arterial and venous thromboembolism in atherosclerotic young women.^{1,10,11}

Wramsby et al., have found higher prevalence of factor V Leiden mutation among primary habitual abortus patients but couldn't find a significant difference between factor II G20210A or MTHFR C677T mutation carriers and controls. They reported higher risk for primary habitual abortus patients compared to secondary ones.¹² We found our patients to have MTHFR defect and carrier (heterozygote) state for α -fibrinogen-455 G-A mutation, but couldn't find other etiologic factors for thrombophilia.

MTHFR is an important enzyme in folate metabolism. Mutation in this enzyme, the most common of which is C677T polymorphism, results in decrease in the activity of the enzyme. As a result, 5-methyl THF levels are decreased and 5,10-methyl THF as well as plasma homocysteine levels are increased.^{13,14} Increased homocysteine levels are reported to be a risk factor for thrombosis and it's well understood that clinical results of this situation are widespread. Severe MTHFR defect, where hyperhomocysteinemia and homocysteinuria develop, might result in peripheral neuropathy, retardation development, hypotonia, stroke and thrombosis. On the other hand, mild MTHFR defect is pretty common in general population and accepted as a risk factor for arterial disorders.¹⁵

Nelen et al., reported that MTHFR C677T mutation increase plasma homocysteine levels which in turn results in 2-3 times increase in the frequency of recurrent spontaneous abortion.¹⁶ Successive studies reported very much increase in plasma homocysteine levels in patients with MTHFR C677T homozygote TT variant that is significantly associated with recurrent spontaneous abortion. In contract, some studies reported C677T polymorphism was not a risk factor for fetal losses.¹⁷ Recent meta-analysis, also suggested no relationship between recur-

rent spontaneous abortion and C677T variant state.¹⁸

Data on the effect of MTHFR gene mutations on idiopathic recurrent spontaneous abortion are still controversial. Some investigators report MTHFR mutations among risk factors for idiopathic fetal losses. Others reported high prevalence of homozygote variant state in recurrent spontaneous abortion but still others couldn't find a relationship between MTHFR mutations and fetal losses and moreover reported similar or lower prevalence of MTHFR mutation among idiopathic pregnancy losses compared to controls.^{5,8} In our cases, both patients were found to have heterozygote MTHFR defect and both responded the treatment successfully. Thus we believe that even heterozygosis for MTHFR defect can cause spontaneous abortion alone or in combination with unknown factors. This accompanying unknown factor might be heterozygote α -fibrinogen-455 G-A mutation that we found in both of our patients. Studies about this mutation reported especially high incidence of ischemic stroke in these patients.¹⁹

Conclusion

Further studies are needed to confirm whether MTHFR defect combined with α -fibrinogen-455 G-A mutation definitely increase risk of spontaneous abortion. Folic acid supplementation and enoxaparin might be helpful, as in our patients, in the management of these patients.

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