Türk Kadın Sağlığı ve Neonatoloji Dergisi

To cite this article: Urel Demir G, Guler Donmez H, Fadiloglu E, Unal C, Cagan M, Utine GE, Beksac MS. Impaired DNA methylation associated adverse gestational outcomes: A case report. Turk J Womens Health Neonatol 2020; 2(4): 140-142

Case Report

Impaired DNA methylation associated adverse gestational outcomes: A case report

Bozulmuş DNA Metilasyonuyla İlişkili olumsuz gebelik sonuçları: Olgu sunumu

Gizem Urel Demir[1], Hanife Guler Donmez*[2], Erdem Fadiloglu[3], Canan Unal[3], Murat Cagan[3], Gulen Eda Utine[1], Mehmet Sinan Beksac[3]

[1]Department of Pediatric Genetics, Hacettepe University, Ankara, Turkey
[2]Department of Biology, Hacettepe University, Ankara, Turkey
[3]Department of Obstetrics and Gynecology, Hacettepe University, Ankara, Turkey

Abstract

The methylenetetrahydrofolate reductase (MTHFR) gene encodes an enzyme called MTHFR involved in DNA methylation and chromosome segregation. MTHFR polymorphisms are associated with DNA methylation disorders including congenital malformations and chromosomal abnormalities, and various obstetrical complications such as miscarriage, fetal growth retardation, preeclampsia, preterm labor, etc. Herein, we have reported a patient with compound heterozygous MTHFR polymorphisms in whom the different type of adverse pregnancy outcomes (1. blighted ovum, 2. preterm delivery, and 3. pregnancy with a fetus having anencephaly and meningocele going together with 46, XX, del (13) (q22)) were observed in her previous three pregnancies. She was referred to our hospital during her third pregnancy for prenatal diagnosis. Her fourth baby was born healthy at 37th gestational week after having necessary precautions. Low dose low molecular weight heparin and low-dose acetylsalicylic acid were added to patient-specific management protocol immediately after the confirmation of her fourth pregnancy. In conclusion, DNA methylation enzyme pathway disorders are associated with adverse gestational outcomes.

Key words: Methylenetetrahydrofolate reductase polymorphisms; DNA methylation; premature birth; 13q deletion syndrome; neural tube defects

Öz

Metilentetrahidrofolat redüktaz (MTHFR) geni, DNA metilasyonu ve kromozom ayrılması süreçlerinde yer alan MTHFR adı verilen bir enzimi kodlar. MTHFR polimorfizmleri, konjenital malformasyonlar ve kromozomal anomalilerini içeren DNA metilasyon bozuklukları ve abortus, fetal büyüme geriliği, preeklampsi, erken doğum, vb. gibi çeşitli obstetrik komplikasyonlarla ilişkilidir. Çalışmamızda compound heterozigot mutasyonu olan ve önceki üç gebeliğinde kötü obstetrik sonuçları (1. blighted ovum, 2. preterm doğum ve 3. anensefali ve meningoseli, 46, XX, del (13) (q22) ile birlikte seyreden bir fetus ile gebelik) olan bir hasta değerlendirilmiştir. Hastanın dördüncü bebeği gerekli önlemleri aldıktan sonra 37. gebelik haftasında sağlıklı doğdu. Dördüncü gebeliğin doğrulanması takiben düşük doz düşük moleküler ağırlıklı heparin ve düşük doz asetilsalisilik asit hastaya özgü yönetim protokolü çerçevesinde başlandı. Sonuç olarak, DNA metilasyon enzimi yolu bozuklukları, olumsuz gebelik sonuçları ile ilişkilidir.

Anahtar kelimeler: Metilentetrahidrofolat redüktaz polimorfizmleri; DNA metilasyonu; erken doğum; 13q delesyon sendromu; nöral tüp defektleri

Corresponding author*: Hanife Guler DONMEZ, Department of Biology, Faculty of Science, Hacettepe University, Ankara, Turkey
E-mail: hnftnr@gmail.com
ORCID: 0000-0002-7413-4939
Received: 17.10.2020 Accepted: 24.12.2020
DOI: 10.46969/ezh.805121

1. Introduction

The 5,10-Methylenetetrahydrofolate reductase (MTHFR) is a regulatory enzyme involved in methionine-homocysteine and folate metabolisms (1). In humans, MTHFR is an approximately 75 kDa enzyme comprising of 656 amino acids and encoded by the MTHFR gene mapped on 1p36.22 (2). This enzyme converts 5,10-methylenetetrahydrofolate to 5- methyltetrahydrofolate which is used by methionine synthase in homocysteine methylation to methionine. Then, methionine is converted to S-adenosylmethionine for DNA methylation. This reaction connects folate metabolism to DNA synthesis, and this enzyme is at the crossroads of the methylation pathways (2). Thus, MTHFR polymorphisms seem to be associated with impaired DNA methylation, and are related to the structural and chromosomal abnormalities of the fetus (3).

Role of MTHFR in diseases was first demonstrated by Mudd et al. (4). This enzyme's deficiency was reported as a reason for occlusive vascular disease, neural tube defects, cholelithiasis/urolithiasis and acute leukaemia (2). MTHFR polymorphisms are also reported to be related to obstetric and perinatal complications (2). Homocysteine is a cellulo-toxic amino acid and is one of the main risk factors responsible for destroying the cellular components of intervillous space (syncytiotrophoblasts, endovascular trophoblasts, superficial epithelial cells of the decidua, endothelial cells of spiral veins, etc.) especially in pregnancies having MTHFR polymorphisms. The entrance of the cellular components of these cells into maternal circulation stimulates maternal innate and humoral immune systems and causes inflammatory processes at the placenta. Meantime, fetal perfusion is affected and obstetric/perinatal complications (miscarriages, fetal growth retardation, preterm deliveries, preeclampsia, ablatio placenta, etc.) occur (2,5). Besides, abnormalities in the DNA methylation pathways cause chromosomal and structural anomalies, as mentioned above (2,3).

With this, we reported a pregnancy with compound heterozygote polymorphism (both MTHFR C677T and A1298T) having three previous pregnancies with adverse outcome (1. blighted ovum, 2. preterm delivery, and 3. pregnancy with a fetus having anencephaly and meningocele). Her 4th and last pregnancy were delivered successfully by applying necessary precautions for the risk factors.

2. Case report

The patient was a 34-year-old woman whose gravida was four, and parity was two. Her first pregnancy was blighted ovum and aborted spontaneously. Unfortunately, abortion material could not be evaluated for chromosomal abnormalities. Her second pregnancy was complicated by preterm contractions and ended up at 36th gestational week via emergency cesarean section. This is a retrospective analysis of an obstetric history (Hacettepe University Local Ethics Committee with reference number GO 19/1064). This manuscript did not comprise identification information and performed according to the Declaration of Helsinki.

She was referred to our hospital during her third pregnancy for prenatal diagnosis. Her third pregnancy was diagnosed with anencephaly and meningocele and fetal chromosome analysis obtained by chorionic villi sampling revealed 46, XX, del (13) (q22). The pregnancy was terminated at 14th gestational week.

Cytogenetic analysis of the patient and her husband revealed normal karyotype results. She was investigated for hereditary thrombophilia and MTHFR polymorphisms. Both MTHFR C677T and A1298C polymorphisms were detected (compound heterozygosity). She was accepted to a pre-conceptional follow-up program before having her fourth gestation.

The patient was registered in a special antenatal care program after getting pregnant (fourth pregnancy). Low dose low molecular weight heparin (LMWH = enoxaparin 2000 anti-Xa IU/0.2 mL) was added to patient-specific management protocol due to anti-inflammatory, anti-migratory, and anti-thrombotic properties (vitamins B1, B2, B3, B6, B9, and B12 daily, methionine restricted diet, 100 mg acetylsalicylic acid) immediately after clinical confirmation of the pregnancy (1,5). Pregnancy follow-up consisted of serial ultrasonography to evaluate fetal growth, aneuploidy screening (triple test), fetal anatomy scanning at the 20th–24th gestational weeks, and non-stress test performed weekly after the 28th gestational week. Gestational diabetes (GDM) was determined by oral glucose challenge test at 24th gestational week. The patient took necessary dietary precautions for GDM. Her fourth baby was born healthy at 37th gestational week via cesarean section. The baby weighed 3,810 g and the Apgar scores were 9, 10, 10 at 1 min, 5 min, and 10 min, respectively.

3. Discussion

The MTHFR gene encoding an enzyme called methylenetetrahydrofolate reductase plays a crucial role in DNA methylation and chromosome segregation. The presence of compound heterozygosity for MTHFR variants 677C/T and 1298A/C can lead a 40-50% reduction in enzyme levels (6). MTHFR polymorphisms have been associated with congenital abnormalities such as NTDs and chromosomal abnormalities leading to miscarriages and obstetrical complications (2).

In the present study, we have reported a patient with MTHFR polymorphisms whose pregnancies were complicated by congenital anomaly, chromosomal abnormality and obstetrical complication (preterm delivery). The first conception of our patient occurred as a blighted ovum, while we were not able to assess the chromosomal condition of miscarriage material. A blighted ovum, also known as an anembryonic pregnancy, is a

common cause of early pregnancy loss that is characterized by the implantation of a fertilized egg with the lack of embryonic development, resulting in an empty gestational sac. The most common cause of early miscarriages is chromosomal abnormalities, substantially numerical aberrations including autosomal trisomies, monosomy X, and polyploidies (7). Chromosomal abnormalities have been reported in about half of early abortions and 85% of miscarriages due to blighted ovum (6). Otherwise, the prevalence of recurrent abortions due to blighted ovum has been detected higher among the consanguineous marriages compared to unrelated marriages, whilst normal karyotype was found in these groups 97.7% and 83.4%, respectively, suggesting an underlying genetic etiology including single gene defects rather than chromosomal imbalances (8). Additionally, contributions of MTHFR polymorphisms to the early pregnancy loss including blighted ovum have been demonstrated (2).

It has been reported that MTHFR polymorphisms were associated with poor obstetrical outcome such as fetal growth restriction, preterm delivery and preeclampsia (1). Second pregnancy in this case was preterm delivery due to preterm contractions and fetal distress. Hyperhomocysteinemia is a metabolic risk factor for placental inflammation which goes together with the destruction of cellular structures of the intervillous space causing obstetrical complications such as preterm deliveries (2).

The third pregnancy of our patient necessitated termination which was diagnosed with NTD attributed to MTHFR polymorphisms, and the fetal karyotype analysis revealed a distal 13q deletion. Besides, terminal deletions of chromosome 13q have been associated with an increased risk of NTD (9). Furthermore, Luo et al. stated that deletions involving chromosome 13q33q34 might be responsible for the occurrence of NTD, emphasizing the haploinsufficiency for the genes located on this chromosome segment (10). Conversely, Lurie et al. argued that the larger deleted chromosomal intervals disrupting 13q22 segment might underlie the pathogenesis of NTD (9).

She was accepted to a pre-conceptional follow-up program before having her fourth gestation. The patient was registered in a special antenatal care program after getting pregnant (fourth pregnancy) and treated as described above. Her fourth baby was born healthy at 37th gestational week via cesarean section.

In conclusion, chromosomal abnormalities, congenital anomalies and obstetrical complications are expected to be observed in pregnancies with MTHFR polymorphisms. This report emphasizes the efficacy of preconceptional assessment of MTHFR polymorphisms in suspected cases to improve pregnancy outcomes.

Declaration of Interest: No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, shareholding and similar situations in any firm.

Source of Finance: During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

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