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A successful treatment with 5 methyltetrahydrofolate of a 677 TT MTHFR woman suffering premature ovarian insufficiency post a NHL (non-Hodgkin's lymphoma) and RPL (repeat pregnancy losses)

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Introduction

Methylation is an ubiquitous regulatory biochemical process in cellular physiology. It is involved in immune response, neurotransmitter function, trans-membrane transport and DNA repair. But it also plays a mandatory role in gene expression regulation and silencing via imprinting and epigenesis, two processes totally dependent upon methylation of DNA and histones. These two last biochemical regulations are of major importance in gametogenesis and early embryo development. The folate cycle is a major partner in methylation: it allows the regeneration of methionine from homocysteine post methylation via SAM (S Adenosyl Methionine) the ubiquitous co factor of Methylation (see fig.1). MTHFR is a strong effector of the folate cycle, but its genetic variants, 677CT and 1298AC, exert a reduced enzymatic activity. Besides being implicated in circulatory and cardiac problems and cancer, these variants exert a strong correlation with the impairment of reproductive functions including male gametogenesis [1], early and late embryogenesis [2, 3], trophoblast development and implantation [4, 5] and may be involved in recurrent pregnancy losses (RPLs) [6, 7]. Non-Hodgkin lymphoma (NHL) is also strongly correlated with these SNPs [8] High doses of folic acid are not an answer for these problems: the synthetic folic acid (Pteroyl Glutamic acid) has a poor capacity to enter the folate cycle to form Tetrahyydrofolate (THF) [9] and then 5 MTHF the active compound necessary for the recycling of Hcy (see fig.1). This leads the occurrence in circulation of UMFA, unmetabolized folic acid syndrome, which may have very negative effects including a flair up of some tumors (Colorectal, prostate). This report reviews the case of a female patient who had RPLs and premature ovarian insufficiency following treatment for NHL. After discovering the homozygous mutation for MTHFR T677 T, the patient was treated successfully with 5 MTHF and delivered a healthy male baby.

Case description

BL Gravida2, Para0, Abortus2, presented when she was 34 years old, on March of 2017. Her menstrual onset was on March 1995. She had been on oral contraceptives from 2000 to 2014. She had her first miscarriage on June 2015 at 12 weeks of gestation and after being on a long-term vitamin supplementation with folic acid. The vitamins were interrupted when she was diagnosed with primary mediastinal diffuse large B cell lymphoma (non-Hodgkin's), on July 2015. From August 2015 to December 2015 she was treated with a combination of drugs known as R-EPOCH, which consists of rituximab, etoposide phosphate, prednisone, vincristine sulfate (Oncovin), cyclophosphamide, and hydroxydaunorubicin. While undergoing chemotherapy she was also treated with a LHRH agonist. After NHL remission, prenatal vitamins containing folic acid were resumed. She had a second miscarriage on October 2016, at 7 weeks of gestation.

On March 2, 2017, she had her first evaluation with us. We found an AMH value at 0.007 nG/mL. Pelvic ultrasound revealed hypotrophic ovaries with a functional cyst on the right ovary measuring 20 and then 24 mm and no

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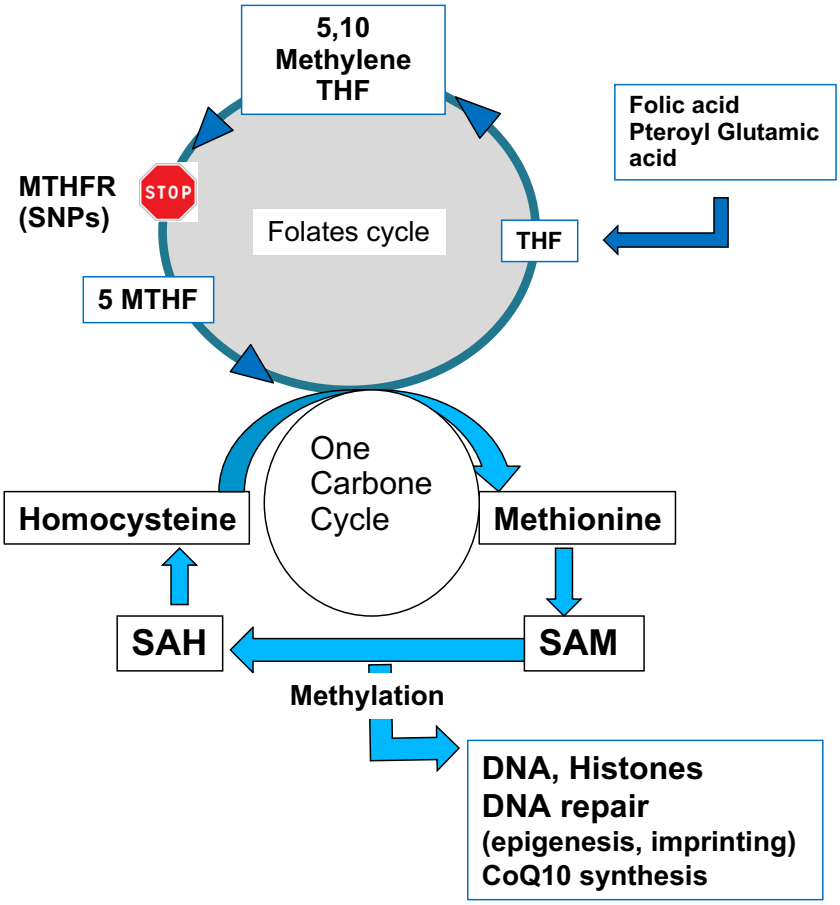

Fig. 1 The one carbon cycle and the folate cycle. 5 MTHF, 5 methyltetrahydrofolate; MTHFR SNP, methylene tetrahydrofolate reductase single nucleotide polymorphism; SAH, S adenosyl homocysteine; SAM, S adenosyl methionine; THF, tetrahydrofolate

antral follicle, but a normal size uterus. The left ovary was atrophic with a volume of 1.91 mL and two antral follicles. Hysterosalpingography showed bilateral tubal patency. She was diagnosed with premature ovarian insufficiency and the couple was counseled DHEA 25 mg three times a day. On April 2017, her basal body temperature (BBT) showed a very short luteal phase of 6–7 days: on day 19, her estradiol was 287 ηG/L and her progesterone at 3.13 μG/L. On September 2017, her AMH was consistently low: <0.003 and she was found to be homozygous for MTHFR C677T variant with a normal serum homocysteine (9.1 μmoles/L). She was asked to discontinue all supplementation with folic acid and was started on methylfolate 800 mg daily and vitamin B complex and B12 [10, 11]. Three months later, she conceived spontaneously. On November 2017, at 5 weeks of gestation, the ultrasound revealed the presence of two intrauterine sacs with one yolk sac each, with one mean sac diameter (MSD) of 9 mm and the other MSD of 13 mm. On December 2017, she had a follow-up ultrasound that showed one gestational sac with a yolk sac and a fetal heart tone; the diagnosis of vanishing twin was made. She was monitored with biophysical profiles every 2 weeks starting at 32 weeks of gestation, but at 36 weeks of gestation she was found to have oligohydramnios and preeclampsia. She had an AFI (amniotic fluid index) of 4.1 and was hospitalized for observation and IV fluids. By 37 weeks, she was delivered by C-section due to oligohydramnios, preeclampsia, and breech presentation. A healthy male baby of 2.69 kg was delivered. The patient has been breastfeeding and she was advised to continue to take 5-MTHF and vitamin B complex while lactating and for the rest of her reproductive life.

Discussion and conclusion

This case report is in line with the occurrence of association between habitual abortions and MTHFR mutations. NHL occurrence in this patient seems also linked her MTHFR SNP background; as this SNP also affects negatively gametogenesis, early and late embryonic development [2, 11], a correlation might be established with our observation. This also means that "complex patients" (including RPLs) should be tested for MTHFR mutation, possibly before oocyte donation attempts [12]. As observed here, homocysteine level is a

weaker marker as its value does not necessarily correlate with the MTHFR genetic background. Indeed, some carriers may enjoy a compensated metabolism (normal homocysteine) in standard conditions but may undergo a pathological imbalance at time of increased metabolic demand, as it is the case for gametogenesis and embryo development.

As documented elsewhere [13], treatment with a support of the one carbon cycle may improve ovarian quality in some patients, as it allows improvement in gametogenesis [10]. In this respect, 5 MTHF is a very interesting tool when the problems are dependant of MTHFR deficiency. It allows to by-pass the mutated enzyme and avoids the issues from high doses of the synthetic folic acid that may cause the occurrence of UMFA and pseudo-MTHFR syndrome, i.e., a blockade of the one carbon cycle due to the competition of folic acid with the natural substrate 5 MTHF. High doses of folic acid may indeed induce an increase in the circulating homocysteine [14]: it is not a good therapeutic option. As also shown by the work of Enciso et al. [2], a MTHFR-correct testing of the patient, followed by a treatment with 5 MTHF, could avoid the need for pre-implantation genetic screening (PGS), an expensive and invasive ART procedure, supposed to remedy unexplained RPLs.

References

1. Gong M, Deng W, He T, Shi Z, Huang G, et al. MTHFR 677C>T polymorphism increases the male infertility risk: a meta-analysis involving 26 studies. PLoS One. 2015;10(3):e0121147.
2. Enciso M, Sarasa J, Xanthopoulou L, Bristow S, Bowles M, Fragouli E, et al. Polymorphisms in the MTHFR gene influence embryo viability and the incidence of aneuploidy. Hum Genet. 2016;135:555–68.
3. van der Put NMJ, Blom HJ. Neural tube defects and a disturbed folate dependent homocysteine metabolism. Eur J Obstet Gynecol Reprod Biol. 2000;92:57–61.
4. Serman L, Dodig D. Impact of DNA methylation on trophoblast function. Clin Epigenetics. 2011;3:7.
5. Branco MR, King M, Perez-Garda V, Bogutz AB, Caley M, et al. Maternal DNA methylation regulates early trophoblast development. Dev Cell. 2016;36:152–63.
6. Unfried G, Griesmacher A, Weismüller W, Nagele F, Huber JC, Tempfer CB. The C677T polymorphism of the methylenetetrahydrofolate reductase gene and idiopathic recurrent miscarriage. Obstet Gynecol. 2002;99:614–9.
7. Yang Y, Luo Y, Yuan J, Tang Y, Xiong L, Xu MM, et al. Association between maternal, fetal and paternal MTHFR gene C677T and A1298C polymorphisms and risk of recurrent pregnancy loss: a comprehensive evaluation. Arch Gynecol Obstet. 2016;293:1197–211.
8. He J, Liao XY, Zhu JH, Xue WO, Shen GP, et al. Association of MTHFR C577T and A1298C polymorphisms with non-Hodgkin lymphoma susceptibility: evidence from a meta-analysis. Sci Rep. 2014;4:6159.
9. Bailey SW, Ayling JE. The extremely slow and variable activity of dihydrofolate reductase in human liver and its implications for high folic acid intake. Proc Natl Acad Sci U S A. 2009;106:15424–9.
10. Dattilo M, D Amato G, Caroppo E, Ménézo Y. Improvement of gamete quality by stimulating and feeding the endogenous antioxidant system: mechanisms, clinical results, insights on gene-environment interactions and the role of diet. J Assist Reprod Genet. 2016;33:1633–48.
11. Servy EJ, Jacquesson-Fournols L, Cohen M, Menezo YJR. MTHFR isoform carriers. 5-MTHF (5-methyl tetrahydrofolate) vs folic acid: a key to pregnancy outcome: a case series. J Assist Reprod Genet. 2018.
12. Jacquesson-Fournols L, Servy EJ, Dale B, Clement A, Menezo Y. MTHFR testing in ART should be compulsory in both male and female patients including oocyte donation programs. J Gynecol Women's Health. 2017 MS Id 555706.
13. Silvestris E, Cohen M, Cornet D, Jacquesson-Fournols L, Clement P, Chouteau J, et al. Supporting the one-carbon cycle restores ovarian Reserve in Subfertile Women: absence of correlation with urinary bisphenol a concentration. Biores Open Access. 2017;6:104–9.
14. Cornet D, Clement A, Clement P, Menezo Y. High doses of folic acid induce a pseudo MTHFR syndrome in a wild type patient: a case report. Sage Open Med Case Rep. 2018.