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IMPORTANCE OF FOLATE EXCHANGE ON THE FORMATION OF CONGENITAL MALFORMATIONS OF THE FETUS

Yangibayeva D. T.

Yuldasheva D. Yu.

Sadikova D.R.

Irnazarova D. X.

Djumayeva F.R.
Tashkent Medical Academy,
Department of Obstetrics and Gynecology No. 2, Tashkent Uzbekistan.

Abstract
The problem of prevention of complicated course of pregnancy and childbirth takes a leading place in modern obstetrics and perinatology. The authors conducted a profound analysis of numerous clinical studies in the area of folate metabolism in general, its role in the reproductive health of women, gestational complications, and the formation of fetal pathology.

Keywords: folate metabolism, genetics, homocysteine, fetal malformations.

Introduction

Protecting the health of a pregnant woman and her unborn child is one of the priorities of modern medicine, but the prevalence of pregnancy complications remains high, increasing the risk of adverse outcomes for a woman's health and perinatal losses. The cause of the complicated course of pregnancy is disorders associated with the folate cycle, caused by endogenous and exogenous factors. Exogenous risk factors include low socio-economic status, unbalanced nutrition, insufficient intake of trace elements and vitamins, alcohol consumption, smoking, etc. Endogenous factors are primarily represented by the peculiarity of the genome, including polymorphisms of genes regulating folic acid metabolism. Defects in folic acid metabolism in the body can be distinguished into a separate group of causes that complicate pregnancy. The folate cycle is a complex process controlled by enzymes that have folic acid derivatives as coenzymes. This acid is a complex molecule consisting of a periodic acid and one (monoglutamate) or several (polyglutamates) glutamic acid residues. Food, especially fresh greens, liver, yeast and some fruits mainly contain reduced polyglutamates, which must be hydrolyzed by the enzyme pteroylpolyglutamate hydrolase to

monoglutamate so that they can be absorbed in the proximal small intestine. After absorption, folate-monoglutamate is reduced to tetrahydrofolate, a compound with biological activity. After methylation, folates enter the blood in the form of 5-methyltetrahydrofolate, which penetrates into cells through endocytosis with the participation of specific folate receptors. Inside the cell, 5-methyltetrahydrofolate serves as a donor of methyl groups and the main source of tetrahydrofolate. The latter acts as an acceptor of a large number of mono-carbon fragments, turning into different types of folates, which, in turn, serve as specific coenzymes in a number of intracellular reactions, in particular, during the synthesis of purines and the pyrimidine base of thymine. One of the reactions requiring the presence of 5,10-methylenetetrahydrofolate and 5-methyltetrahydrofolate is the synthesis of methionine from homocysteine. Remethylation of homocysteine to methionine catalyzes the cytoplasmic enzyme methionine synthase (MTR). The enzyme requires methylcobalamin, a derivative of vitamin B12. Methionine synthase catalyzes the methylation of homocysteine into methionine through a reaction in which methylcobalamin acts as an intermediate carrier of the methyl group. In this case, cobalamin is oxidized, and the MTOR enzyme goes into an inactive state. Restoration of enzyme function is possible during the methylation reaction with the participation of the enzyme methionine synthase-reductase (MTRR). The donor of the methyl group in this case is the activated form of methionine – S-adenosylmethionine, which is also used for methylation of other compounds: DNK, RNK, proteins and phospholipids. A key role in the synthesis of methionine from homocysteine is played by the enzyme 5.10-methylenetetrahydrofolate reductase (MTHFR), which reduces 5.10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which carries the methyl group necessary for the remethylation of homocysteine. The metabolic consequences of folic acid deficiency is an increase in homocysteine levels. There are also genetic defects in the production of enzymes that catalyze the transition of folic acid into its active form, necessary for the remitylation of homocysteine into methionine. The most studied mutation is C677T of the MTHFR gene, associated with the substitution of cytosine for thymine at position 677, causes the replacement of alanine with valine (p.Ala222Val) in the catalytic domain of the protein-enzyme, leading to a decrease in its activity in the homozygous variant of the polymorphic allele by 70%, in heterozygous genotypes – by 35%. Homozygosity for the C677T allele leads to a significant increase in homocysteine levels, especially against the background of low folate content in blood plasma. It is the decrease in the activity of this enzyme that is one of the important reasons for the accumulation of homocysteine in the body. In recent years, numerous proofs have been obtained that homozygous (TT) and even heterozygous (CT) genotypes are much more common among women with complicated pregnancy. Deficiency of folic acid and B vitamins associated with the peculiarities of the diet or with their insufficient assimilation by the body, as well as defects in the genes of folate metabolism, causing reduced enzyme activity, lead to

excessive accumulation of homocysteine in the blood and disruption of methylation processes in the cell. Homocysteine has a pronounced toxic property, while the negative effects it has are very diverse. Homocysteine is a derivative of the essential amino acid methionine. Methionine, obtained from food as part of a protein, participates in all reactions where the methyl group is used for the synthesis of biologically active substances (nucleic acids, adrenaline, creatinine, etc.).
Goal. To evaluate the contribution of polymorphic variants of folate cycle genes to the disruption of early stages of human embryonic development.

Materials and Methods

30 pregnant women with various types of fetal malformations in the maternity complex of the clinic of the Tashkent Medical Academy, who made up group 1, were analyzed. Group 2 consisted of 30 women with a history of undeveloped pregnancy. The comparison group consisted of 30 patients with normal fetal development. The studied groups did not differ in age, parity, onset of menstrual function, presence of genital and extragenital pathology. In all pregnant women, the level of homocysteine and folic acid in blood plasma was determined, a molecular genetic study of peripheral blood was performed (DNA isolation; detection of genetic mutations in the genes of the folate cycle MTHFR, MTRR, MTR).

Results and their Discussion

The level of homocysteine in the blood plasma of pregnant women in the control group was 5.61 (4.8 – 6.77) mkmol/l. In the plasma of women of groups 1 and 2, there was a higher level of homocysteine of 20.8 and 17.5 mmol/l, respectively, than in the patients of the comparison group. In women of groups 1 and 2, homozygous mutation occurred in 11 (36.7%) and 8 (26.7%) cases, respectively, and in 18 (60%) and 16 (53%) — heterozygous mutation of the MTHFR C677T gene. And in the control group, only a heterozygous mutation of this gene was detected in 4 women. When studying the MTHFR gene, the mutation was detected in 14 (46.6%) and 13 (43%) women of groups 1 and 2, respectively, which is 7.7 and 6.5 times higher than the control group. The level of folic acid is 5.3 ng/ml in group 1 and 9.8 and 13.5 in group 2 and control groups, respectively, which is not lower than normal values (>3 ng/ml).

Conclusion

Thus, experiments show that mutations of the MTHFR gene and hyperhomocysteinemia are more common in women with a history of fetal defects and undeveloped pregnancies. The study of polymorphism of only one gene of methylenetetrahydrofolate reductase (MTHFR C677T) is not enough, a comprehensive study of the issue is necessary, with genotyping according to other indicators of the folate cycle and their components. The occurrence of

hyperhomocysteinemia in these women, despite normal folic acid levels, indicates that folic acid is insufficiently metabolized due to mutations in the folate cycle genes. Pathogenetically justified early diagnosis and timely correction of imbalance changes with a personalized approach at the stages of pre-pregnancy preparation and early ontogenesis to reduce the risk of complicated pregnancy.

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