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Folic acid and its implications in genetic pathology

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Abstract

Vitamins are essential for the proper functioning of the body, and Folic Acid, also known as Vitamin B9, has many benefits for the body. Folic Acid contributes to the normal development of the fetus, preventing the risk of fetal birth defects, mainly represented by neural tube defects and orofacial clefts. At the same time, Folic Acid deficiency can cause serious health problems. That is why it is necessary to know the roles of Folic Acid in the body, the symptoms of Folic Acid deficiency, but also what foods are rich in Folic Acid and how to supplement the body's need for Folic Acid.

Keywords: Folic Acid; MTHFR C677T gene mutation; Pregnancy; Down Syndrome; Neural tube

1. Introduction

Vitamins are essential for the proper functioning of the body, and Folic Acid (FA), also known as Vitamin B9, has many benefits for the body. At the same time, FA deficiency can lead to health problems. That is why it is necessary to know the roles of FA in the body, the symptoms of FA deficiency, but also what foods are rich in FA and how to supplement the body's need for FA.

2. Folic Acid: nomenclature, chemical composition, important roles, daily necessities

FA, the pteroylmonoglutamic acid, also known as Vitamin B9, is a water-soluble B-complex Vitamin with important roles in cell proliferation in the body [1]. It is synthesized by microorganisms and some plants. Boiling food destroy this vitamin [2]. FA is essential for the synthesis and multiplication of cellular genetic material.

The daily requirement of FA is 100-200µg/day, but it increases in case of pregnancy, malnutrition, and malabsorption [3].

FA supplementation is often talked about during pregnancy and lactation, but this vitamin is essential for all people.

The chemical structure of FA includes a pteridine nucleus, para-aminobenzoic acid, and glutamic acid. In various foods, folates are conjugated with polyglutamic acid (Fig. 1), [4].

This complex promotes intestinal absorption of the vitamin. Under the enzymatic action, polyglutamate is converted to mono and diglutamate, which can be rapidly absorbed in the proximal jejunum [5, 6].

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In plasma, it is found in the form of N5 methyltetrahydrofolate (N5 MTHF), from where it is transported to the cell by a specific transport molecule [7]. Once in the cell, N5 tetrahydrofolate is converted to polyglutamate after removal of the N5 group methyl under the action of the Vitamin B12 [8]. Under this form (polyglutamate), folate is retained by the cell intervening in the metabolism of purines and stimulating cell division (Fig. 2), [9].

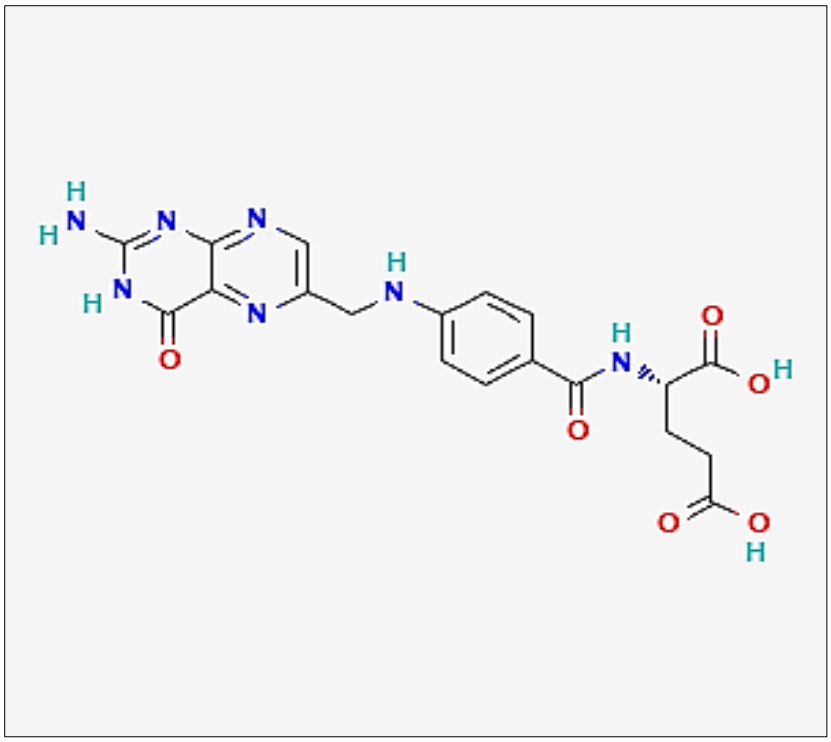

Figure 1 Folic Acid chemical structure [4]

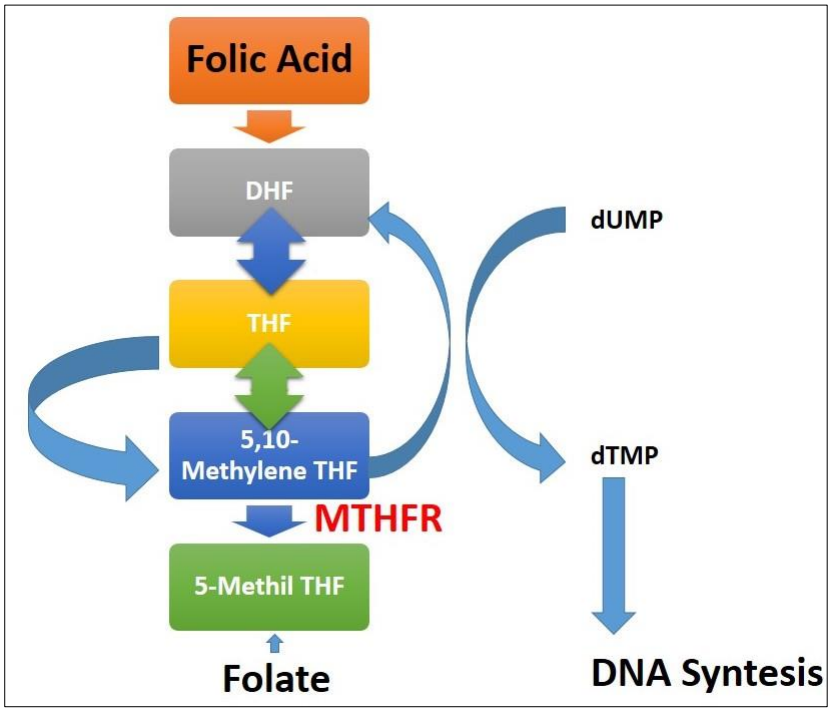

Figure 2 Folic Acid metabolism

DHF, dihydrofolate; THF, tetrahydrofolate; THF, tetrahydrofolate; dUMP, deoxyuridine monophosphate; dTMP, thymidylate; MTHFR, methylenetetrahydrofolate reductase [9].

3. Folic Acid deficiency

Folic Acid deficiency can have the following four important causes:

3.1. Increased body's need for FA (pregnancy, chronic hemolytic anemia, malignancy, myelofibrosis)

It has been observed that in tissues with a high rate of cell division, such as hematoforming bone marrow and the epithelium of the intestinal mucosa, a higher amount of folate is required [10].

FA deficiency can lead to megaloblastic anemia, thrombocytopenia or changes in the intestinal and lingual mucosa [11].

In pregnant women, the level of folate decreases due to the requirements of the developing body, the intense proliferations that have Ioc during embryonic and fetal growth and therefore, it is necessary to supplement the exogenous intake of FA with foods rich in this vitamin, or with vitamin as such [12].

Decreases in folate levels have been reported during periods of growth of the body, in childhood and adolescence, when a FA supplement is needed [13].

3.2. Alcoholism

Distilled alcohol does not contain FA, while beer and wine contain this acid. In addition, alcohol can interferes with the normal metabolism of FA by disrupting it [14].

3.3. Malnutrition

People who eat mostly potatoes may have FA deficiencies. FA intake can also be disrupted in drug users, people with severe or debilitating mental illness who are generally malnourished [15].

3.4. Malabsorption (celiac disease, jejunal resections, tropical sprue)

There are syndromes of intestinal malabsorption of folate, hereditary folate malabsorption, characterized by folate deficiency due to impaired intestinal folate absorption and impaired folate transport into the central nervous system (CNS), in which case it is necessary to supplement with FA in the diet of the patient with this condition, or by parenteral injection in case of severe deficiency [16].

4. Folic Acid and pregnancy

Few women know that during pregnancy, the body's need for FA increases and that its lack can be the cause of serious malformations of the development of the neural tube in the fetus [12, 17].

The main cause of folate deficiency in pregnancy is an increase in DNA and RNA synthesis, associated with the development of the fetus, placenta, and uterus, but also an increase in the mother's erythrocyte mass [18, 19]. It has been calculated that during a normal pregnancy the need for folate increases about three times [12]. For this reason, a group of American doctors and psycho-sociologists have set up a National Program to popularize the importance of increasing the consumption of FA during pregnancy, in order to prevent the occurrence of malformations of the CNS [20, 21].

Based on these findings, the National Center for Toxicological Research (CNCT) of the Food and Drug Administration (FDA) has taken the initiative to supplement the content of wheat flour and pasta with FA [22]. Thus, it was recommended to add 140 g of FA to every 100 g of flour to enrich with this important vitamin a staple food in the daily diet [23].

In these investigations, it was found that some mothers who gave birth to children with Down syndrome had an imbalance in folate metabolism due to a mutation in an important gene, *MTHFR (*methyltetrahydrofolate reductase) *mutation*, called the *MTHFR C677T mutation.*

Natural source high in folate are: beef, liver, boiled spinach, black-eyed peas, asparagus, brussels sprouts, lettuce, avocado, broccoli, mustard greens, green peas, kidney beans, canned tomato juice, Dungeness crab, orange juice, dry-roasted peanuts, fresh orange and grapefruit, papaya, banana, hard-boiled egg, cantaloupe [24-26].

5. MTHFR C677T gene mutation and maternal risk of Down Syndrome

Down syndrome is due to the excess of genetic material belonging to extrachromosome 21 [27]. Clinically, Down syndrome can be defined as a syndrome with characteristic dysmorphia, saturated hypotrophy and severe mental retardation [27-29].

The additional chromosome 21 is of maternal origin in 95% of cases and is caused by the failure of the chromosomes of the pair 21 during meiosis [27, 30, 31].

The risk of giving birth to a child with Down syndrome increases with the mother's age [28]. Thus, the risk of mothers under 29 is 1 / 3,000 births, at 30 it increases sharply to 1/700, and at 45 the risk is almost unacceptable, being 1/40 of births [28, 31-33].

These statistics show that young mothers have a lower risk of giving birth to children with Down syndrome [29]. However, there is a fairly high percentage of such young mothers, whose cause of chromosome 21 failure is more difficult to explain and has long been unknown [27]. To clarify this situation, a team of researchers from Arkansas (USA) conducted a study and was found that women who gave birth to children with Down syndrome had a defect in FA metabolism related to folate methylation, a hypomethylation of the DNA molecule and a high risk of abnormal segregation of the chromosome 21 pair [34, 35]. Thus, the mutation of the gene encoding the enzyme methylene tetrahydrofolate reductase (MTHFR) that these young women had was discovered. Gene mutation consists of C-T substitution at nucleotide number 677 of the gene for MTHFR [36-40].

MTHFR gene polymorphisms affect 25% of Hispanic people, 10% of white and Asian people, and 1% of African Americans [41]. Thus, the mutation of the gene encoding the enzyme *methylenetetrahydrofolate* reductase (*MTHFR*) that these young women had was discovered. Gene mutation consists of C-T substitution at nucleotide number 677 of the gene for *MTHFR [36-40].*

MTHFR gene polymorphisms affect 25% of Hispanic people, 10% of white and Asian people, and 1% of African Americans [41].

As an indicator of mutation was used: the investigation of the relationship between plasma homocysteine and methionine, as well as cytotoxicity of methotrexate.

In women with the C677T mutation in the *MTHFR gene,* there is an increase in homocysteine levels as well as an increase in the cytotoxicity of methotrexate. These women were 2.6 times more likely to give birth to a child with Down syndrome than those without a mutation [42].

These results implicate FA deficiency (due to the effect of the *MTHFR gene mutation*) on the etiology of chromosome 21 nondisjunction in young women under the age of 29, at whom the risk of Down syndrome is generally low (1/3,000 births) [43].

As a result, it is necessary to supplement the prenatal intake of FA, especially in pregnant women at risk of Down syndrome and neural tube defects, as well as careful monitoring of the diet of pregnant women, in which the intake of FA is not neglected in the first trimester of pregnancy [44]. It is necessary to promote this attitude by family doctors and specialists who are directly involved in prenatal follow-up of pregnancy, as well as in genetic counseling offices, in order to prevent malformations of the CNS in the fetus.

6. Conclusion

Folic Acid, part of the Vitamin B-complex, contributes to the normal development of the fetus, preventing the risk of fetal birth defects, mainly represented by neural tube defects and orofacial clefts.

AF, the synthesized form of Vitamin B9, quite difficult for the body to assimilate naturally, actively participates in cell proliferation being an essential nutrient for oral health.

Compliance with ethical standards

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Authors E.-A.R. and Ş.-D.A. contributed in data curation and software and formal analysis. C.-C.A and D.-F.A. contributed in project administration, validation and supervision.

Disclosure of conflict of interest

The authors declare no conflict of interest. All authors read and approved the final version of the manuscript.

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