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Editorial Open Access

Folic Acid Supplementation in Prevention of Neural Tube Defects

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Editorial

Neural tube defects (NTDs) are congenital anomalies (CAs) of the central nervous system. They are the most common birth defects along with congenital heart anomalies (CHAs) and anomalies of urinary system. EUROCAT (European Surveillance of Congenital Anomalies) reported that a total prevalence of major congenital anomalies was 23.9 per 1000 births in the period 2003-2007. CHAs were the most common non-chromosomal subgroup (6.5/1000), followed by limb defects (3.8/1000), anomalies of urinary system (3.1/1000) and nervous system anomalies (2.3/1000) [1].

CAs are a special category of human disorders due to their very early onset and defect condition. Therefore there is a limited chance for complete prevention of it. NTDs are the most frequent CAs of the central nervous system. However, this has been a great progress in the prevention of NTDs with periconceptional folic acid (FA) or FA-containing multivitamins (MVs). NTDs is defined as a group of severe CAs of the central nervous system resulting from failure of the neural tube to close during neurulation between 20 and 28 days after conception. Wide world, the birth prevalence of NTDs (spina bifida and anencephaly) varies among different populations. In some areas, such as Northern China, the prevalence is very high (1/200) [2].

The neurulation is major step in brain development, who involves the formation of the first well-defined neural structure (neural tube). The neural tube forms during the third week of gestation (20-28 day) [2,3]. The neurulation is the embryonic process that leads to the ultimate development of the neural tube. This process can be divided into two phases:

Primary neurulation (3–4 week): involves the formation of the brain and neural tube from the caudal region to the upper sacral level [4]. This phase of neurulation is associated with open NTDs and result in conditions including anencephaly, myelomeningocele (open spina bifida) and craniorachischisis [5].

Secondary neurulation completes the distal sacral and coccygeal regions [4]. Disruption of secondary neurulation results with skin covering lesion sites of the spinal cord structure such as asymptomatic spina bifida occulta and severe spinal cord tethering are classed as closed NTDs [5].

NTDs are associated with very poor life. Twenty percent of fetuses die in utero (stillbirths or therapeutic abortions). The remainder of individuals survives beyond the first week of life with approximately 10% of individuals die within the first year. Those living beyond this period will generally have a life with poor health and repeated medical and surgical interventions and physiotherapy [6].

The origin of NTD can be explained by the interaction of genes and environmental factors (dietary deficiency). The occurrence of NTDs is most frequent in the condition of low maternal socioeconomic status. Also, there are some clinical factors and conditions which increased the risk of NTDs or other FA–sensitive CAs. These conditions are: patients with specific genotypes associated with higher risk of NTDs, previous pregnancies with NTDs or family history of NTDs, malabsorption disorders (inflammatory bowel disease), obesity (BMI >35 kg/m^2), diabetes, compliance and life style issues. Also, an increased risk of NTDs has patients who take antiepileptic drugs, folate antagonists (methotrexate, sulfonamides), cigarettes, and those who belong to high-risk ethnic groups (Sikh, Celtic, Northern Chinese) [7]. Humans cannot produce folate. The major dietary sources of folates are fresh and frozen green leafy vegetables, citrus fruits and juices, liver, wheat bread, and legumes such as beans. Thus the requirement of this water-soluble vitamins is supplied partly by dietary intakes of folates [6,8,9].

Folate (vitamin B9), is one of the 13 essential vitamins. It cannot be synthesized de novo by the body, and must be obtained either from diet or supplementation. Dietary folate is a naturally occurring nutrient found in foods such as leafy green vegetables, legumes, egg yolk, liver, and citrus fruit. Folic acid is a synthetic dietary supplement that is present in artificially. Neither folate nor FA is metabolically active. Both must be reduced to participate in cellular metabolism. L-5-Methyltetrahydrofolate (5-MTHF; L-methylfolate) is the predominant micronutrient form of folate that circulates in the plasma and that is involved in the biologic process. After dietary intake FA can absorb directly, while folate is changed into the monoglutamate form by conjugase enzymes. For folate metabolism that involves FA, this synthetic form of the vitamin must first be converted to the natural form tetrahydrofolate (THF), which is converted to 5, 10-MTHF and 5-MTHF. After meat, fish or plant intake, amino acids (methionine) are released. Methionine is converted to homocysteine, which is toxic metabolite. Humans neutralize it very soon. But the neutralization requires vitamin B12 as a cofactor and 5-MTHF as a methyl donor. These explain the value of folate/FA deficiency in the etiology of NTDs. Also, the very important cause of hyperhomocystenemia and/or lack of methionine is the polymorphism of the MTHF-reductase gene. The lower activity of the MTHF-reductase enzyme reduces the production of 5-MTHF and increases the levels of homocysteine. This is a possible cause of a delay in the closure of the neural tube, and subsequently NTDs [6]. Hyperhromocysteinemia is one of the leading causes for NTDs [8].

Closure of the neural tube during development is a complex, but also an unclear process. NTDs is a multifactorial disorder, and the etiology of it including genetic and environmental factors. The importance of the maternal folate status for the NTDs-risk was first suggested more than 50 years ago [10].

Many studies show that preconceptional intake of supplemental FA can reduce the incidence of NTDs by as much as 70% in some populations. These results led to mandated fortification of all enriched cereal grain products with FA in the United States beginning in 1996

to ensure that women of child-bearing age would consume adequate quantities of the vitamin. Although FA fortification has decreased NTD incidence in some subpopulations, fortification has not completely eliminated NTDs [11].

One of the largest studies was the Study of Hungarian Periconception Service conducted in 1984. Half of the participants were supplied with micronutrient combination (12 vitamins: FA 0.8 mg, B12 4.0 mg, B6 2.6 mg, B2 1.8 mg, four minerals and three trace elements). The other half of participants were supplied a placebo. The participants used the supplements at least for one month before conception and at least two months after it (critical period for NTDs). This study showed the efficacy of these MVs in the reduction of CAs, especially for cardiovascular CAs. The efficacy of 0.4 mg FA was shown in a Chinese-US study. There was 79% reduction in the risk of NTDs in areas with high rates of NTDs [6].

The World Health Organization recommended supplemental dose of 0.4 mg of FA per day in prevention of NTDs. If supplementation is started after the first trimester of pregnancy it will not help prevent birth defect [12]. Diet rich with folate is an important factor for prevention of NTDs, but can't completely neutralize the risk for CAs. Women with polymorphism in the folate cycle have higher requirements than other women. FA fortification of the food couldn't archive optimal folate level in the plasma. So, supplementation in pre-conceptional period at the moment is the best way to improve the folate status within a relatively short time (4-12 weeks) [13].

When we are talking about folate supplementation there are some questions: Which choice is better: FA or MVs? FA or Methylfolate? What about food fortification? 50% of all pregnancies are unplanned-what about it?

The use of MVs containing FA and other B vitamins in several studies showed high efficacy in the reduction of NTDs (about 90%), then the use of high or low dose of FA alone. This MV combination is effective for the reduction of some others CAs. When hyperhomocysteinemia is the cause of NTDs, vitamins B12, B2 and B6 are very important cofactors in folate-homocysteine metabolism [14].

After their intake, natural folate and synthetic FA are converted to 5-MTHF. A nature-identical folate of 5-MTHF as 6S-5-MTHF has been synthesized as a calcium salt and marketed as Metafolin. At present, the use of 6S-5-MTHF seems to be better than the use of FA in several aspects: it does not mask B12 deficiency, it's already a biologically active form, it doesn't cause unmetabolized FA in blood, and it's absorbed and utilized at least as well as FA. Although there are no clinical trials on the effectiveness of 5-MTHF in preventing NTDs, metabolic studies have shown that 5-MTHF is a biologically active form of the vitamin and it seems to be at least as effective as FA in improving folate biomarkers. The literature clearly shows that a better food folate intake is associated with better folate markers and that food folate can prevent NTDs (by increasing folate status) [6,13-15].

The major problem is that about 50% of pregnancies are unplanned in the USA, Hungary, and many other industrialized countries. If women have unplanned pregnancies and they haven't used supplements, they can't take advantage of this preventive method during the pre-conceptional period. At the time of the first missed menstrual period and on about the 15th post-conceptional day, when the possible pregnancy is recognized, the neural tube is preparing to close. Mandatory food fortification with FA to increase intake, as done in the United States and other countries, has not yet been introduced in any European country [6,13-14,16].

Conclusion

Primary prevention of congenital anomalies in the population based on controlling environmental risk factors is a crucial policy priority, including preconceptional care and whole population approaches. This editorial wants to promote an adequate prevention of NTDs, but also the prevention to the other CAs. It's necessary to educate young women on the appropriate use of FA and MV supplementation at least one month before conception and at least two month after it.

Recent studies showed that about 90% of NTDs are preventable this way [6]. There are three possible uses of this new primary preventive method for the prevention of NTDs: dietary intake of folate, preconceptional supplementation of FA and MVs and flour fortification with FA, which is not used in Europe [14].

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