Folic Acid and Epilepsy

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Folic acid has been a topic of discussion within the epilepsy community for several decades. Folic acid was initially suspected to be epileptogenic (1), but that concern has been resolved, as research has demonstrated that folic acid in less than supraphysiologic concentrations does not promote seizures. Epileptologists are now concerned that folic acid may be too low in persons with epilepsy taking some antiepileptic drugs (AEDs). Low serum and red blood cell levels of folic acid in women of childbearing potential increase the risk of fetal birth defects. For men and women, low levels of folic acid are associated with elevated homocysteine and an increased risk for cardiovascular disease. A convincing argument now develops that routine folic acid supplementation is important for women and men receiving AEDs.

What Does Folic Acid Do?

Folic acid is a carrier of hydroxymethyl and formyl groups and is involved in the synthesis of purines and thymine, required for the formation of DNA. The conversion of homocysteine to methionine requires the enzyme methionine synthetase and uses methyltetrahydrofolate as a methyl donor and vitamin B12 as a cofactor. Folic acid promotes cellular growth and maturation of red blood cells, and deficiency of folic acid is associated with reduced growth and with a megaloblastic anemia.

How Is Folic Acid Obtained?

Folic acid is present in fresh green vegetables, liver, yeast, and some fruits. Cooking reduces folate content by as much as 90%. Most individuals in the United States consume 50 to 500 μg of folic acid, in part provided by the folic acid supplement in grain, which was mandated by the Centers for Disease Control in 1998.

What Are the Effects of AEDs on Folic Acid?

Men and women receiving some AEDs are at risk for low levels of serum and red blood cell folic acid. Serum and red blood cell folate are reduced in up to 90% patients receiving phenytoin (PHT), carbamazepine (CBZ), or barbiturates (2). AEDs that do not induce cytochrome P450 enzymes are not associated with low levels of folic acid. Lamotrigine (LTG), an AED that has weak folate properties in vitro, had no effects on serum or red blood cell folate in 14 patients on short-term treatment and in an additional 14 patients who had been treated for up to 5 years (3). Patients on zonisamide (ZNS) had serum folate levels that were no different than controls (4).

Data on valproate (VPA) effects on folic acid are conflicting. Most authors report that valproate does not reduce folate levels (4,5) but may interfere with folate metabolism by inhibiting glutamate formyl transferase, an enzyme mediating the pathway that produces folinic acid (6).

What Happens When Folic Acid Levels Are Low?

Folic acid deficiency is associated with elevated levels of homocysteine, and this phenomenon appears to be prominent in those receiving enzyme-inducing AEDs (7,8). Homocysteine levels are elevated both at fasting and after methionine loading in persons receiving CBZ, PHT, phenobarbital (PB), and primidone (PRM) (9). Adults receiving VPA, an inhibitor of cytochrome P450 enzymes, had lower homocysteine levels fasting and after methionine loading than did controls (9), although children on VPA had low folic acid and elevated homocysteine levels (10). In one study of persons receiving CBZ or PHT for epilepsy, folic acid levels were lowest and homocysteine levels highest in persons homozygous for a common mutation in the methylenetetrahydrofolate gene (11). This suggests that drug-gene interactions may predict folate and homocysteine changes in response to AEDs.

What Are the Clinical Consequences of Low Folate and Elevated Homocysteine?

Folic acid deficiency is classically associated with megaloblastic anemia but is rarely associated with neurological abnormalities unless accompanied by a deficiency of B12 as well (pernicious anemia). Folate deficiency induced experimentally in animals

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by folate antagonists or by a folate-deficient diet produces intrauterine growth retardation and congenital malformations, even with a period of deficiency as short as 2 days early in gestation (12). In women with epilepsy, low serum and red blood cell folate levels are associated with an increased incidence of spontaneous abortions and malformations (2,13–15).

Hyperhomocysteinemia is associated with vascular disease, including cerebrovascular disease, and may also be associated with neurodegenerative disease (16). Supplementation with folic acid, vitamin B6 (pyridoxine hydrochloride), and vitamin B12 (cyanocobalamin) readily normalizes homocysteine levels (16).

Neural tube defects (anencephaly and spina bifida) are more frequent in children born to mothers with low folic acid and B12 levels and high homocysteine levels. In one study, women with fetuses with neural tube defects had lower B12 as well as folate levels (17). A second study found that mothers of children with neural tube defects had significantly elevated homocysteine levels (18). The defect may be related to abnormalities in the activity of the enzyme methionine synthetase. Methionine synthetase is critical for methylation in a number of biologic processes, including the production of myelin basic protein and DNA biosynthesis. Both folate and B12 are required as cofactors for methionine synthetase. VPA-mediated neural tube defects are postulated to be related to VPA effects on methionine synthesis and DNA hypomethylation via inhibition of methionine synthetase (19).

What Are the Effects of Supplementation with Folic Acid?

Supplementation with folic acid appears safe even up to doses as high as 15 mg/day. The U.S. Food and Drug Administration has directed that oral tablets of folic acid not exceed 1 mg because of concerns brought forward more than 30 years ago that folic acid in large amounts might counteract the antiseizure effects of AEDs and increase the seizure frequency in some children (20). Although that concern is no longer held by epileptologists, the dosage restriction persists.

Folate may protect against birth defects by overcoming an abnormality in homocysteine metabolism. Occurrence (21–23) and recurrence studies (24,25) have conclusively shown that folate supplementation significantly reduces the risk of neural tube defects in children born to nonepileptic women. The risk of occurrent neural tube defects is reduced by 60% with doses as low as 0.4 mg/day (23) and the risk of recurrent neural tube defects reduced by 72% with a 4 mg/day supplement (25). The occurrence of other major malformations (except cleft lip and palate) is also reduced by periconceptional folate supplementation (26).

A dose-response effect of plasma folate levels on neural tube defects was demonstrated in a large case control study of women giving birth in Ireland (27). Serum and red blood cell folate were determined at a median of 15-weeks gestation. Although risk was highest in women with RBC folate levels of less than 340 nmol per L (150 ng/mL), there was a continuous gradation of risk, suggesting that folate supplementation may have a wide-reaching benefit. These data suggest that folate supplementation in women with RBC folate levels of less than 340 nmol/L will reduce the risk of a neural tube defect by more than 85%.

How Should Folic Acid Be Provided?

Folate must be present within the first 25 days postconception in order to protect against malformations of the neural tube. A missed menstrual cycle is usually not noticed until the 15th-day postconception. Forty percent of pregnancies are unplanned, and 50% of women with planned pregnancies do not consult a health care provider prior to conception (28).

Therefore, folate supplementation should be given routinely to women of childbearing potential. The Canadian College of Medical Geneticists recommend that 0.8 to 5.0 mg/day of folic acid be given to women who are at increased risk of having offspring with neural tube defects and who are planning a pregnancy (29). The United States Public Health Service recommends that all women of childbearing age in the United States capable of becoming pregnant consume 0.4 mg/day of folic acid for the purpose of reducing their risk of having a child affected with a neural tube defect (30). Women who have already had a child with a neural tube defect are encouraged to consult their physician regarding appropriate folate dosage and to refer to the 1991 Centers for Disease Control guideline suggesting a dosage of 4 mg/day, based on the MRC recurrent risk study.

Whether women with epilepsy require a higher dose than 0.4 mg/day is not known. The American College of Obstetric and Gynecologic Physicians educational bulletin (1996) recommends preconceptional folic supplementation for women with seizure disorders (31), and the American Academy of Neurology practice parameter (1998) recommends routine supplementation of folic acid 0.4 mg to 4 mg/day for women of childbearing potential receiving AEDs (32,33). However, these recommendations may not be routinely incorporated into clinical practice. Certainly before the American Academy of Neurology and American College of Obstetric and Gynecologic Physicians' recommendations were issued, it was not common practice to provide folic acid before conception and not even during all pregnancies. In the United Kingdom, 67% of those attending an antenatal clinic for the first time were unaware of recommendations regarding folate supplementation, and only 37% of those who were aware had received that information prior to conception (34). In one retrospective

evaluation of care practices in women with epilepsy delivering at a U.S. teaching hospital in 1994 to 1995, gestational folic acid supplementation was not documented for one fourth of the women (35). A survey conducted in 1998 by the Epilepsy Foundation of care providers likely to encounter women with epilepsy found that only 24% of family practice providers provided routine folic acid supplementation to women with epilepsy on AEDs, and only 19% of neurologists did so (36). Only 17% of the 3535 medical practitioners responding to the knowledge-based survey knew the recommended dose of folic acid supplementation.

Based on currently available information, it seems prudent to ensure that men and women with epilepsy receiving AEDs, particularly enzyme-inducing AEDs, receive adequate folic acid. For most individuals, this is best accomplished by providing a dietary supplement. Supplementation can be provided by prescription-strength folic acid tablets (1 mg each) or as part of a multivitamin supplement. Most multivitamins contain 0.4 mg of folic acid. Over-the-counter prenatal vitamins contain 0.8 mg folic acid, and prescription prenatal vitamins contain 1 mg of folic acid.

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