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Review

Valproate and folate: Congenital and developmental risks

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ABSTRACT

Increasing awareness of the congenital and developmental risks associated with the use of sodium valproate (VPA) has led to recent European guidelines designed to avoid the use of this drug in pregnancy if effective alternative treatments are available. In the general population, it is well established that periconceptual folic acid reduces the risk of neural tube defects (NTDs) and possibly other congenital abnormalities.

We here review the evidence 1) that VPA interferes with one-carbon metabolism, including the transport of methylfolate into the brain and the placenta by targeting folate receptors; 2) that VPA effects on the folate metabolic system contribute to congenital and developmental problems associated with VPA exposure; and 3) that genetic factors, notably polymorphisms related to one-carbon metabolism, contribute to the vulnerability to these VPA-induced risks.

Based on these facts, we propose that the standard periconceptual use of 400 μg of folic acid may not adequately protect against VPA or other antiepileptic drug (AED)-induced congenital or developmental risks. Pending definitive studies to determine appropriate dose, we recommend up to 5 mg of folic acid periconceptually in at-risk women with the caveat that the addition of supplementary vitamin B12 may also be prudent because vitamin B12 deficiency is common in pregnancy in some countries and is an additional risk factor for developmental abnormalities.

1. Valproate, congenital and developmental risks

A considerable body of evidence has accumulated over many decades indicating that maternal exposure to any AED during pregnancy is associated with an increased risk of fetal congenital abnormalities, including neural tube defects (NTDs) [1]. The risk varies between drugs, but the greatest and increasing concern relates to VPA, which carries a risk of up to 10%, several fold above the background risk [2,3].

More recently, evidence of more subtle neurodevelopmental harm to children exposed to this drug during their gestation has grown. At 3 and 6 years of follow-up, fetal exposure to VPA was associated with a reduced IQ of 7–10 points compared with exposure to carbamazepine, lamotrigine, and phenytoin [4,5]. Valproate exposure was also associated with worse verbal and memory abilities compared with exposure to other drugs and reduced nonverbal and executive functions compared with lamotrigine exposure. In the case of VPA, these cognitive deficits were, in part, dose-related, but no dose-related effects were observed with the other drugs [4,5]. Reports suggesting that VPA increases the risk of autism spectrum disorder and attention-deficit hyperactivity disorder (ADHD) by 3- to 5-fold [6,7] are also of concern. In one prospective observational multicenter study in the USA and UK, which enrolled pregnant women with epilepsy on AED monotherapy over a 5-year period, children of mothers who took VPA during their pregnancy were at a significantly greater risk of a diagnosis of ADHD [7]. Taking into account all developmental problems, it has been estimated that 30 to 40% of preschool children who had been exposed to VPA in utero may be affected [2]. In view of the greater risk to a fetus associated with the use of VPA compared with the use of other AEDs during pregnancy, there are good reasons to avoid the use of VPA in women who have the potential to become pregnant. There are, however, some unavoidable exceptions to this advice, as summarized by Angus-Leppan et al [3,8]. We here review the role of folate in relation to these VPA risks.

2. Folate status and congenital malformations

It is well established that in the general population, periconceptual adequacy of folate status can reduce the risk of NTDs, so much so that up to 80 countries have introduced mandatory fortification of cereals and grains with folic acid which has been associated with a risk reduction of 20–60% (overall about one-third) depending on the background risk [9,10]. Some argue

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for an even greater exposure to folate to improve outcomes [9]; others argue for the addition of vitamin B12 to improve the benefits and reduce the risk of harm from excessive folate in the presence of vitamin B12 deficiency, evidence of which has been steadily mounting [10–12]. The mechanisms of the reduced risks of NTDs with folic acid are uncertain, but it is clear that folates are crucial to the healthy development of the fetus, especially, but not exclusively, the nervous system. There is plausible but limited evidence that folic acid supplementation also lowers the risk of other congenital malformations including orofacial clefts and cardiac defects, as well as limb defects, abdominal wall defects and urogenital defects [13]. Despite the well-publicized benefits of periconceptual folic acid, many unplanned and even planned pregnancies overlook this advice, and these include some women with epilepsy.

3. Mitigation by folate of neurodevelopmental risks associated with AED use in pregnancy

In the prospective observational multicenter study of Meador et al. [5], it was notable that at 6 years of follow-up, periconceptual folic acid exposure was associated with a higher IQ compared with no folic acid exposure for each of the 4 AEDs studied, including VPA. For all 311 children in the study, periconceptual folic acid was associated with an average of 5 point higher IQ [5]. Other studies [14,15] have found a dose-dependent increased risk of language delay after VPA exposure in utero. In the large prospective Norwegian mother and child cohort study, periconceptual folic acid exposure prior to and during the first trimester was associated with a 4-fold reduction in the risk of delayed language skills at eighteen months in the children of mothers exposed to many different AEDs including VPA [16]. This study also found a correlation between high maternal VPA concentration and low language scores at eighteen months. These authors noted that women in Norway are recommended to use 0.4 mg folic acid daily in the periconceptional period only, while women with epilepsy who use AEDs usually are recommended to use 1 to 5 mg daily in the periconceptional period and 0.4 mg daily in the second and third trimesters [16].

In similar Norwegian mother and child cohorts [17,18] and in other studies [19,20], periconceptual folic acid also reduced the risk of autistic traits in children of AED-treated mothers and of mothers without epilepsy or exposure to AEDs.

4. The effects of valproate and other AEDs on folate biochemistry and one-carbon metabolism

In the 1960s and 1970s, many studies revealed widespread evidence of folate deficiency in children and adults with epilepsy on treatment with the older barbiturate and hydantoin (e.g., phenytoin) AEDs [21,22]. Treatment with folic acid for up to 1–3 years was associated with an improvement in the mental state of many of these patients especially in mood, drive, and sociability [22]. The earliest study of VPA monotherapy in patients with newly diagnosed epilepsy again noted a rise in red cell volume (MCV) and fall in red cell folate at one year of follow-up, indicative of an impairment of functional folate status [23].

Subsequent evidence from experimental models of epilepsy in rats indicated that AEDs had profound but variable effects on folate uptake in the brain. Valproate lowered brain folate levels and partially blocked the reuptake of folinic acid [24]. In this respect, it was very similar to phenobarbital [25]. Although phenytoin also lowered brain folate, it did not block reuptake, whereas carbamazepine had little effect on folate [24]. Recently, Rubinchik-Stern et al. [26] perfused normal full-term human placentas with VPA for 180 min leading to a reduction of placental folate by 25–35%. They found that VPA altered mRNA levels of major carriers for folate, glucose, choline, and some hormones. They concluded that VPA targets the folate receptor FOLR1, and possibly other folate receptors, leading to direct inhibition of placental folate uptake. Earlier, Fathe et al. [27], utilizing cell culture modeling, concluded that VPA is a noncompetitive inhibitor of high affinity folate receptors such as folate receptor α (FRα). It has also been suggested that the drug may interfere with folate metabolism by inhibiting glutamate formyl transferase, an enzyme mediating the pathway that produces 5-formyltetrahydrofolate (folinic acid) [28]. Fig. 1 illustrates how reduced folate derivatives of folic acid, i.e., formyl-, methylene-, and methyltetrahydrofolate in association with vitamin B12 play an important role in one-carbon metabolism providing both the carbon residues for de novo nucleotide synthesis and the methyl groups necessary for the formation of S-adenosylmethionine (SAM). The latter is required for the methylation of numerous vital compounds, including the cytosine residues of DNA and nuclear histones, thus influencing epigenetic control of gene expression [29,30].

In a review and meta-analyses of 8 studies, Ni et al. [31] confirmed that VPA monotherapy in epileptic subjects is consistently associated with an increase in plasma homocysteine levels. Most of these studies also reported a fall in serum folate levels. Vitamin B12 levels were unaffected. Whether elevated homocysteine plays a role in the neurodevelopmental abnormalities that occur with AED use or is merely a marker of a disturbance in the remethylation pathway of homocysteine metabolism is not known. In a study of their own, Ni et al. [32] again confirmed a rise in homocysteine levels associated with VPA monotherapy, not observed with lamotrigine. Both VPA and lamotrigine were associated with reduced levels of serum folate which also correlated positively with the methylation status of peripheral blood methylenetetrahydrofolate reductase (MTHFR) amplicons. They suggested that both drugs may induce specific regions of DNA hypomethylation. Earlier, Smith et al. [33] reported decreased methylation scores across CpG islands in 50 neonates exposed in utero to a variety of AEDs including VPA, but mostly lamotrigine, particularly in those with the longest exposure.

It is evident that genetic factors contribute to the vulnerability to VPA and other AED-induced congenital abnormalities [34]. The occurrence of NTD in a first pregnancy significantly increases the risk in subsequent pregnancies. The risk of congenital abnormalities was 3 to 4 times higher for mothers with epilepsy who were homozygotic for the MTHFR 677TT variant compared with those with wild type MTHFR 677CC homozygotes [35]. Some authors have suggested that the C677T MTHFR gene mutation increases the risk of hyperhomocysteinemia in patients with epilepsy on AED therapy [36,37], but in a study of 498 patients on different AEDs, Semmler et al. [38] concluded that raised homocysteine levels were predicted by folate and vitamin B12 levels but not by the 7 polymorphic variants of genes related to homocysteine metabolism that they examined. In a recent comprehensive review of genetic risk factors for folate-responsive NTDs, Molloy et al. [34] concluded that little progress had been made searching for specific risk-causative variants in candidate genes and therefore more complex genetic interactions and epigenetic mechanisms need to be explored to explain this important gene-nutrient interaction.

5. Preventive measures

The growing evidence and awareness of the congenital and developmental risks associated with the use of VPA has led to new European guidelines designed to avoid the use of the drug in pregnancy unless alternative treatments are not available [3,39]. The drug should not be prescribed to women of childbearing potential unless a contraceptive program is also implemented.

As in the general population, periconceptual folic acid supplementation is recommended to women with epilepsy, whether or

not they are on AEDs, but there are no recommendations as to the dose and no randomized controlled trials upon which to base clear recommendations. Indeed, such trials would be precluded on ethical grounds. It may be insufficiently appreciated that, as reviewed here, VPA has a direct inhibitory action on folate and one-carbon metabolism, thus contributing at least in part to the congenital and developmental risks. Some data does point to an ameliorative effect of higher folic acid intake during the periconceptual period in women with epilepsy who use AEDs on delayed language skills in their offspring [16]. Although more research into the mechanism of this interaction between folate and AEDs, in particular VPA, is urgently needed, there is already some evidence that VPA interferes with the transport of folate, perhaps by targeting folate receptors, leading to a fall in brain and placental folates [24–26].

There is considerable evidence that folate and one-carbon metabolism, including vitamin B12, are crucial to fetal neural tube closure [40], to child brain development, and indeed to brain health at all ages [22,41]. The reduced risks of developmental, cognitive, and language delays by periconceptual folic acid in children exposed to VPA and other AEDs suggested by the studies reviewed here are entirely in keeping with the vital role of this vitamin in brain function and the evidence of perturbation of folate metabolism by AEDs in the causation of impaired neurodevelopment. This association is further supported by the reports that underlying maternal genetic factors relating to the one-carbon cycle also predispose to congenital and developmental risks in infants with intrauterine exposure to VPA and other AEDs [34,36,37]. Although phenobarbitone, phenytoin, carbamazepine, and lamotrigine also interfere with one-carbon metabolism in varying ways and to varying degrees, it is unclear why VPA is associated with the greatest congenital and developmental risks. Whether the inhibitory action of VPA on folate metabolism contributes, at least in part, to its antiepileptic action is beyond the scope of this review, except to add that experimentally, folate derivates at high doses have convulsant properties and can be used in experimental models of epilepsy [22,29].

Folic acid is a synthetic and unnatural form of the vitamin, which after oral administration is reduced and then converted to the active formyl-, methylene-, and methylfolate derivatives (Fig. 1). The latter is the form transported into the nervous system and is limited by a highly efficient active blood–brain barrier mechanism [22,29]. In women on VPA or any other AED that interferes with folate and one-carbon metabolism, it is unlikely that the daily recommended 400 μg of periconceptual folic acid affords adequate protection from the undesirable adverse consequences of these drugs. Although the prospective observational studies reviewed here suggest that folate may mitigate the risk of congenital and neurodevelopmental complications, further controlled studies are much needed, though difficult to justify on ethical grounds considering that the requirement for controls in such studies might suffer detrimental consequences from being randomized to the placebo group. Pending further studies of the protective effects of different doses of the vitamin, including methylfolate, it would seem prudent to recommend up to 5 mg of folic acid daily prior to and during at least the first trimester of any pregnancy in women with epilepsy on VPA or other AEDs. Additionally, since it is estimated that half of pregnancies are not planned, these recommendations on folic acid supplementation should be made at the time of prescription for any AED in women of childbearing age. However, there are also some important caveats (see summary BOX).

It has been known for many decades that prolonged excess folate in the presence of vitamin B12 deficiency may be harmful to the adult nervous system [29]. Furthermore, although less common in women of childbearing potential than in the elderly, it has become increasingly recognized that vitamin B12 deficiency is a significant problem in many countries and may occur at a younger age in certain ethnicities. It is also more common in women whose intake of animal source foods is limited either through poverty or the practice of veganism and vegetarianism. Vitamin B12 levels should therefore always be checked and if necessary treated, particularly because vitamin B12 deficiency is also a risk factor for NTDs [10,41,42]. Disturbingly, an increased risk of facial clefts has been reported in the offspring of the mothers in whom folic acid supplements were continued beyond the first two months of pregnancy [43]. Although adequate periconceptual folic acid protects against autism spectrum disorders, excessive folic acid may increase the risk [44]. These clinical suspicions are reinforced by experimental studies of excessive folate during pregnancy in mice [45]. Because of the widespread consumption of supplements containing folic acid and the addition of supplemental folic acid to breakfast cereals and other ready-to-eat foods, caution should be exercised, particularly in countries that mandate the fortification of cereals and grains with folic acid. Patients receiving controlled higher doses of folic acid as here proposed should be cautioned against the use of additional unregulated supplemental folic acid consumption. For all these reasons, the use of supplemental folic acid during pregnancy should be undertaken with due consideration of the potentially deleterious effects of excessive folate, particularly in the presence of vitamin B12 deficiency, necessitating, at least, assessment of vitamin B12 status and possibly also additional vitamin B12 supplementation.

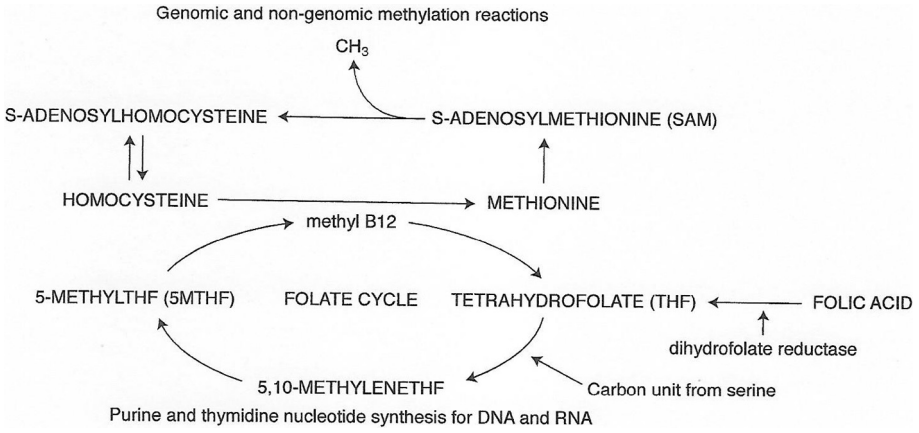

Fig. 1. Relationships between the folate cycle, vitamin B12, methylation, and nucleotide synthesis. Folic acid is a synthetic unnatural form of the vitamin which first must be reduced by dihydrofolate reductase to the natural tetrahydrofolate form to enter the folate cycle. Methylfolate (5-methylTHF) is the active transport form into the nervous system and the placenta. VPA interferes with folate uptake through folate receptors and possibly by inhibition of the enzyme glutamate formyl transferase responsible for the conversion of THF to 5- and 10-formyltetrahydrofolate.

Recommendations for all women of childbearing age taking an AED.

1. Take periconceptual folic acid up to 5 mgs daily i.e. prior to and for the first trimester.
2. The on-going use of additional folic acid containing supplements should be considered in assessing total periconceptual folic acid.
3. Assess vitamin B12 status and administer a vitamin B12 supplement if indicated.
4. In women with a history of a previous NTD or other foetal malformation, carry out genetic screening for abnormalities in one-carbon metabolic pathways and recommend genetic counselling.

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