Seizure 21 (2012) 276–281

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

The effect of vitamin B supplementation on homocysteine metabolism and clinical state of patients with chronic epilepsy treated with carbamazepine and valproic acid

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ARTICLE INFO

Article history:
Received 24 July 2011
Received in revised form 28 January 2012
Accepted 31 January 2012

Keywords:
Homocysteine
Folate
Vitamin B12
AEDs
Supplementation
Clinical state

ABSTRACT

Purpose: To investigate the influence of vitamin B supplementation on the plasma total homocysteine (p-tHcy), serum folate (s-FA), serum B12 (s-B12), and clinical state of patients with chronic epilepsy.
Methods: Beck Depression Inventory (BDI) scores and p-tHcy, s-B12, and s-FA levels were assessed at baseline, after 1 year of supplementation (G1), and before and after 1 year of VPA or CBZ therapy (G2).
Results: Eighty-one patients participated in the study: 51 patients with chronic epilepsy (G1) treated with carbamazepine (CBZ) or valproic acid (VPA), and 30 patients with newly diagnosed epilepsy (G2). At baseline, mean p-tHcy level was significantly higher in G1 than G2 ($p = 0.0001$) with no significant differences in s-FA or s-B12 levels. p-tHcy level significantly decreased in CBZ-treated G1 patients ($p = 0.00002$) after 1 year of supplementation and increased in G2 after 1 year of anti-epileptic drug (AED) therapy without supplementation. BDI scores in G1 decreased significantly after 1 year of supplementation ($p = 0.0001$) and increased significantly in VPA-treated G2 patients after 1 year of AED therapy ($p = 0.02$). The number of hyperhomocysteinemic patients significantly decreased in G1 after vitamin B supplementation ($p = 0.01$) and increased in G2 ($p = 0.002$). We also observed improved BDI scores and reduced seizure frequency in patients with chronic epilepsy.
Conclusions: These data support the hypothesis that AEDs play a major role in hyperhomocysteinemia development in patients with epilepsy. Adding folate and vitamin B12 to AED therapy is a safe and inexpensive way to reduce the risk of hyperhomocysteinemia.

1. Introduction

Epilepsy is a relatively frequent chronic neurologic disorder that often requires lifelong therapy. Therefore, chronic toxicity is an important issue. Previously published data shows that patients with epilepsy receiving chronic anti-epilepsy drug (AED) therapy are more prone than the general population to have hyperhomocysteinemia and low folate levels.[1–3] Recent studies showed that the duration of AED therapy is significantly associated with the acceleration of atherosclerosis in patients with epilepsy.[4–7] Nevertheless, lowering Hcy with folate and other vitamins did not provide any appreciate benefit in preventing cardiovascular and cerebrovascular events.[8,9]

Hyperhomocysteinemia can also reduce the effects of antiepileptic drugs,[10,11] as the convulsant effect of homocysteine has been previously described in an animal model.[12] Increased homocysteine may result in poor seizure control in patients with epilepsy and the development of refractory epilepsy.[12–14] More than 60% of patients with chronic epilepsy have a history of interictal depression. The proportion of patients with depressive mood is higher in refractory epilepsy than in well-controlled epilepsy.[13,15] The increase in plasma total homocysteine (p-tHcy) level could be induced by a significant folate deficiency, which may also be a cause of depressive symptoms in patients with chronic epilepsy.[16–20] Therefore, hyperhomocysteinemia recently has been identified as a risk factor for depression.[16,17,21]

The prevalence of hyperhomocysteinemia, defined as fasting total Hcy greater than 12 μmol/l, is between 5% and 10% in the general population[20] and may be as high as 30–40% in the elderly and up to 40% in patients with epilepsy.[17,22–25] Elevated p-tHcy levels observed in patients with epilepsy is mainly due to the reduced activity of the key enzyme 5,10-methylenetetrahydrofolate

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doi:10.1016/j.seizure.2012.01.013

reductase [MTHFR] caused by polymorphisms in the MTHFR gene[3,12,26,27] and vitamin B deficiency (folate, vitamin B12, or B6), the important cofactors in the metabolism of Hcy, induced by older AEDs, such as carbamazepine, phenytoin, phenobarbital, and primidone.[21,28] Karabiber suggested that valproic acid and carbamazepine (CBZ) significantly increase homocysteine levels compared with controls,[29] and Yoo et al. observed a 25% increase in homocysteine level in patients taking phenytoin and CBZ, but not valproic acid (VPA) compared with controls.[26]

These drugs stimulate many cytochrome P450 (CYP) and glucoronyl transferase (GT) enzymes of liver, and hence the metabolism of folate.[28] Folate, alone or associated with other vitamins, is commonly used to normalize p-tHcy level in patients with epilepsy.[3,24,30,31] Long-term vitamin supplementation may affect both the course of the disease and its treatment.[10,13,17,25,27,30,31]

The aim of the present study was to investigate the influence of vitamin B supplementation on the p-tHcy, serum folate (s-FA), serum B12 (s-B12) levels, as well as the clinical state of patients with chronic epilepsy regarding frequency of seizures and occurrence of depressive symptoms.

2. Material and methods

2.1. Participants

From January 2008 to September 2010, we recruited patients at the First Department of Neurology and outpatient clinic of the Institute of Psychiatry and Neurology in Warsaw, Poland. The study protocol was approved by the local ethics committee and informed consent was collected from all participants. Blood samples were analyzed in the lab of the Department of Clinical Diagnostics of the Institute of Psychiatry and Neurology in Warsaw.

Patients were recruited with the following inclusion criteria: (1) 18–65 years of age in both groups (only four patients in all groups were older than 50 years, but had no history of any comorbidities and fulfilled all inclusion criteria); (2) established diagnosis of epilepsy; (3) duration of epilepsy of at least 2 years in patients with chronic epilepsy; (4) AED monotherapy (CBZ or VAL); (5) no modifications in epilepsy treatment for at least 6 months before entering the study and good participants' drug compliance; (6) no previous exposure to any AEDs in patients with newly diagnosed epilepsy; (7) serum AED levels within the therapeutic range in all patients.

Exclusion criteria (for all participants) were: (1) diseases other than epilepsy or regular drug therapy with medications other than AEDs; (2) any risk factor for atherosclerosis including: smoking, diabetes mellitus, hypertension, hypercholesterolemia; (3) vascular disease, i.e. myocardial infarction, stroke or transient ischemic attack; or (4) other illness, such as: renal dysfunction, thyroid dysfunction, chronic inflammatory diseases, active gastrointestinal disease, anemia, psychiatric illness, alcoholism, cancer and other condition known to interfere with metabolism at the time of sample collection; (4) vegetarianism or a history of a genetic defect of homocysteine, cobalamin, or folate metabolism.

2.2. Methods

Patients' p-tHcy, s-B12, and s-FA levels were measured at baseline in all groups. Blood samples were collected after an overnight fast, cooled on ice immediately, and centrifuged at 4 °C. Serum was separated within 1 h and stored at −70 °C. p-tHcy, s-B12, and s-FA levels were measured with the immunoassay method using commercial kits (Immulite, DPC, United States). Normal reference ranges in fasting conditions were 5–12 μmol/l (tHcy), 3–17 ng/ml (s-FA), and 173–878 pg/ml (s-B12). Hyperhomocysteinemia was defined as a p-tHcy level $\geq$ 12 μmol/l; levels between 12 and 30 μmol/l were defined as moderate hyperhomocysteinemia. Serum AED levels were determined by enzyme-multiplied immunochemical technique.

Patients with epilepsy received a written invitation to participate in the vitamin supplementation trial. Folate (0.4 mg a day), magnesium with 50 mg of vitamin B6, and vitamin B12 (100 μg a day) were administered for 1 year, and p-tHcy, s-B12, and s-FA levels were measured again after 1 year of vitamin B supplementation. In patients with newly diagnosed epilepsy, p-tHcy, s-B12, and s-FA levels were measured before and after 1 year of either VPA or CBZ therapy.

Seizure frequency was calculated by dividing the total number of seizures by the duration of the disease.

The Beck Depression Inventory (BDI) total score was used as a screening instrument for symptoms of depression, and was assessed in patients with chronic epilepsy before and after 1 year of supplementation and in patients with newly diagnosed epilepsy before and after 1 year of VPA or CBZ therapy. A score of >11 points was considered pathological, a score of 12–26 points suggested minor depression, and a score of >27 points indicated major depression.

2.3. Statistical analysis

Data were analyzed using the statistical package Statistica ver. 10 (Statsoft, U.S.A.) and numerical data are depicted as mean ± standard deviation (SD). Statistical analyses of parametric variables were performed with paired and independent two-tailed Student's *t*-tests and with χ^2 or Fisher's exact tests for categorical differences. The Wilcoxon Signed Rank test (for paired samples) and the Mann–Whitney *U*-test (for unpaired samples) were applied when evaluating differences in biochemical parameters and comparisons between treatment groups, respectively. Statistical significance level was set at $p < 0.05$.

3. Results

3.1. Clinical characteristic of patients

The study population consisted of 81 adult patients with epilepsy: 51 patients with chronic epilepsy (G1) and 30 patients with newly diagnosed epilepsy (G2). In the group of 51 patients with chronic epilepsy there were 33 females (64.7%) and 18 males (35.3%) at the age between 18 and 65 years (mean age 39.6 ± 14.3 years). The group of 30 patients with newly diagnosed epilepsy consisted of 19 females (63.3%) and 11 males (36.7%). The mean age of newly diagnosed patients was 29.3 ± 9.4 years (range, 18–65 years). The examined groups of patients (G1 and G2) were sex-matched (F/M 1.7 in G1 and 1.8 in G2), but they were not matched in relation to age, because the aim of the work was mainly focused on analyzing the changes occurring in each group either after 1-year VPA or CBZ treatment with vitamin supplementation in long-term treated patients (G1) or without this supplementation in group of patients with newly-diagnosed epilepsy.

Within the group of patients with chronic epilepsy 22 (43.1%) suffered from partial epilepsy, 8 (15.7%) from partial epilepsy with secondary generalized seizures and 21 (41.2%) from primary generalized epilepsy. The mean duration of treatment in patients receiving AEDs was 14.2 ± 13.7 years (range, 2–50 years). Among patients treated with AEDs, 23 patients (mean age 31.6 ± 10.8 years; 16 females, 7 males) were treated with VPA and 28 patients (mean age 46.3 ± 13.6 years; 17 females, 11 males) were receiving CBZ. Mean daily doses were 991.3 ± 287.5 mg of VPA (range, 800–2000 mg) and 921.4 ± 268.9 mg of CBZ (range, 600–1600 mg).

Table 1
Concentrations of plasma total homocysteine, vitamin B12, and folic acid in patients with chronic (G1) or newly diagnosed (G2) epilepsy at baseline and after 1 year of CBZ or VPA therapy with (G1) or without (G2) vitamin B supplementation.

	Group 1 (G1) Patients with chronic epilepsy ($n=51$) treated with CBZ ($n=28$) or VPA ($n=23$)			Group 2 (G2) Patients with newly diagnosed epilepsy ($n=30$) treated with CBZ ($n=14$) or VPA ($n=16$)			Comparisons between G1 and G2 at baseline
	Before supplementation	After supplementation	p	Before treatment	After treatment	p	p
Homocysteine (μmol/lY± SD)							
All patients	12.6 ± 5.8	10.0 ± 3.0	0.00007	8.8 ± 2.8	11.0 ± 3.5	0.000005	0.0001
CBZ-treated	14.9 ± 6.3	10.7 ± 3.7	0.00002	9.0 ± 2.3	10.6 ± 2.7	0.01	–
VPA-treated	9.8 ± 3.4	9.3 ± 1.4	NS	8.6 ± 3.3	11.4 ± 4.2	0.0001	–
B12 (pg/l ± SD)							
All patients	342.2 ± 154.1	401.3 ± 147.9	0.0008	342.9 ± 137.3	335.7 ± 126.5	NS	NS
CBZ-treated	314.5 ± 153.5	350.5 ± 114.4	NS	323.2 ± 152.1	327.7 ± 156.4	NS	–
VPA-treated	375.9 ± 151.4	463.3 ± 162.4	0.0001	360.2 ± 125.5	342.6 ± 98.2	NS	–
Folate (ng/lY± SD)							
All patients	7.2 ± 3.9	9.3 ± 3.7	0.00005	8.4 ± 3.8	6.2 ± 2.4	0.0003	NS
CBZ-treated	6.2 ± 3.4	9.0 ± 3.0	0.00001	8.2 ± 4.7	6.2 ± 2.5	NS	–
VPA-treated	8.4 ± 4.2	9.7 ± 4.5	0.04	8.5 ± 2.9	6.2 ± 2.3	0.0001	–

Within the group of patients with newly diagnosed epilepsy 13 (43.3%) had partial epilepsy, 2 (6.7%) had partial epilepsy with secondary generalized seizures, and 15 (50.0%) had primary generalized epilepsy. Sixteen (53.3%) patients received VPA and 14 (47.7%) patients received CBZ. Mean maintenance daily doses were 837.5 ± 150.0 mg of VPA (range, 600–1000 mg) and 642.9 ± 85.2 mg of CBZ (range, 600–800 mg).

3.2. Plasma total homocysteine, folate, and vitamin B12 at baseline

At the beginning of the study, mean p-tHcy level was significantly higher in patients with chronic epilepsy than in patients with newly diagnosed epilepsy ($p = 0.0001$; Table 1). However influence of age in patients with chronic epilepsy cannot be excluded. Hyperhomocysteinemia (p-tHcy ≥ 12 μmol/l) was found in 20 (39.2%) patients with chronic epilepsy and in 4 (13.3%) patients with newly diagnosed epilepsy, differences were statistically significant ($p = 0.02$) (Table 2). Among those with chronic epilepsy, hyperhomocysteinemia was found in 16 patients (57.1%) receiving CBZ and 4 patients (17.4%) receiving VPA ($p = 0.001$), and s-FA levels were lower in CBZ-treated patients than in VPA-treated patients ($p = 0.0001$; Table 1). There were no significant differences in s-FA between patients with chronic epilepsy and patients with newly diagnosed epilepsy (Table 1).

Patients' s-B12 levels were similar in both investigated groups. Among patients with chronic epilepsy, CBZ-treated patients had lower mean s-B12 levels than VPA-treated patients; however, this difference was not statistically significant (Table 1).

3.3. Response to vitamin supplementation

3.3.1. Plasma total homocysteine, folate, and vitamin B12 after supplementation in patients with chronic epilepsy

In patients with chronic epilepsy, the number of patients with hyperhomocysteinemia decreased significantly from 20 (39.2%) to 11 (21.6%) after the vitamin supplementation period ($p = 0.01$). Mean p-tHcy level also decreased significantly ($p = 0.00007$), but only in CBZ-treated patients ($p = 0.00002$); differences were not statistically significant in VPA-treated patients (Table 1). The s-FA level increased significantly overall ($p = 0.00005$), as well as specifically among CBZ-treated ($p = 0.00001$) and VPA-treated patient subgroups ($p = 0.04$); a significant increase in s-B12 was observed only in VPA-treated patients ($p = 0.0001$; Table 1).

3.3.2. Plasma total homocysteine, folate, vitamin B12 in newly diagnosed patients after 1 year of VPA or CBZ therapy

After 1 year of treatment, significant increases in p-tHcy were observed in newly-diagnosed VPA-treated ($p = 0.0001$) and CBZ-treated patients ($p = 0.01$). The s-B12 level did not change significantly after treatment, and folate level decreased significantly in VPA-treated patients ($p = 0.0001$). The number of patients with hyperhomocysteinemia increased significantly from 4 (13.3%) to 10 (33.3%) ($p = 0.002$; Table 1).

Table 2
Clinical state of patients with chronic (G1) or newly diagnosed (G2) epilepsy at baseline and after 1 year of CBZ or VPA therapy with (G1) or without (G2) vitamin B supplementation.

	Group 1 (G1) Patients with chronic epilepsy ($n=51$) treated with CBZ ($n=28$) or VPA ($n=23$)			Group 2 (G2) Patients with newly diagnosed epilepsy ($n=30$) treated with CBZ ($n=14$) or VPA ($n=16$)			Comparisons between G1 and G2 at baseline
	Before supplementation	After supplementation	p	Before treatment	After treatment	p	p
Percentage of patients with hyperhomocysteinemia (≥12 μmol/l)							
All patients	39.2% ($n=20$)	21.6% ($n=11$)	0.01	13.3% ($n=4$)	33.3% ($n=10$)	0.002	0.02
CBZ-treated	57.1% ($n=16$)	35.7% ($n=10$)	NS	7.1% ($n=1$)	28.6% ($n=4$)	0.01	–
VPA-treated	17.4% ($n=4$)	4.4% ($n=1$)	0.001	18.8% ($n=3$)	37.5% ($n=6$)	NS	–
Frequency of seizures (meanY± SD per 1 year)							
All patients	10.9 ± 19.9	4.0 ± 8.8	0.0001	6.6 ± 16.4	1.2 ± 2.3	NS	NS
CBZ-treated	12.5 ± 18.5	4.6 ± 7.6	0.001	7.1 ± 18.8	0.5 ± 0.7	NS	–
VPA-treated	9.0 ± 21.7	3.1 ± 10.1	0.03	6.1 ± 14.6	1.8 ± 3.0	NS	–
Beck Depression Inventory (BDI)							
All patients	9.1 ± 6.9	6.9 ± 3.7	0.0001	6.5 ± 5.5	8.3 ± 4.7	0.011	NS
CBZ-treated	9.0 ± 7.9	7.0 ± 4.1	0.02	8.4 ± 7.0	8.8 ± 6.0	NS	–
VPA-treated	9.3 ± 5.6	6.8 ± 3.3	0.0004	4.9 ± 3.1	7.9 ± 3.4	0.02	–

3.3.3. Clinical state of patients with chronic epilepsy after 1 year of vitamin B supplementation

Among patients with chronic epilepsy, seizure frequency before entering the study was 10.9 ± 19.9 overall, 12.5 ± 18.5 in CBZ-treated patients, and 9.0 ± 21.7 in VPA-treated patients. After 1 year of vitamin B supplementation, seizure frequency had decreased significantly (Table 2).

Mild depression (BDI ≥ 11) was observed in 16 (31.4%) patients with chronic epilepsy at baseline. After 1 year of supplementation, the number of patients with BDI ≥11 decreased to 5 (9.8%). There was a significant decrease in BDI score in patients with chronic epilepsy after 1 year of supplementation (overall, $p = 0.0001$; CBZ-treated, $p = 0.02$; VPA-treated, $p = 0.0004$; Table 2). No correlation was found between folate, p-tHcy, or vitamin B12 levels and BDI score for any AEDs administered. The correlations between these variables did not change after supplementation.

3.3.4. Clinical state of newly diagnosed patients after 1 year of AED therapy without supplementation

In newly diagnosed epilepsy patients an increase in BDI score (above ≥11) was observed. There was a significant increase in BDI score in these patients after 1 year of VPA or CBZ therapy ($p = 0.01$); however, this increase was significant only in VPA-treated patients ($p = 0.02$) (Table 2).

4. Discussion

This study confirms earlier observations that mild hyperhomocysteinemia is a common condition in patients with epilepsy receiving old antiepileptic drugs such as CBZ and VPA.[26,29,32] The demonstrated p-tHcy increase was 39.2%, which is similar to results obtained by Vilaseca et al.[33] and higher than observed in the studies of Tamura et al.[32] and Schwaninger et al.[22] We have also demonstrated that after 1 year of treatment with CBZ or VPA, s-FA significantly decreased and p-tHcy significantly increased in adult patients with epilepsy. These findings may support the hypothesis that these AEDs play a major role in the early development of hyperhomocysteinemia in patients with epilepsy.[34,35]

Long-term antiepileptic therapy is associated with mild hyperhomocysteinemia likely caused by vitamin B deficiency, which is more evident in adult patients in epilepsy with a 677C → T mutation of the MTHFR gene.[3,25,30,34,36] This mutation is associated with about 70% reduction in the activity of the MTHFR enzyme.[24] CBZ and VPA as well as other older AEDs affect homocysteine metabolism by reducing MTHFR activity.

In the present study we observed significantly lower levels of s-FA in patients receiving CBZ or VPA than in patients with newly diagnosed epilepsy who had not been exposed to these AEDs. Although the decrease of s-FA in CBZ-treated patients has been presented before,[33,36,37] it should be stressed that in our study, in contrary to observations by Gidal et al.[11] and Vilaseca et al.,[33] s-FA levels also decreased significantly in VPA-treated patients with newly diagnosed epilepsy after 1 year of treatment. AEDs may impair folate absorption and gastrointestinal transport by altering gastrointestinal pH. These drugs may induce folate-catabolizing hepatic enzymes, such as cytochrome P450 and GT.[13,18,28,36] The effect of VPA on folate is probably related to the inhibition of glutamate formyl transferase and the change in balance between various folate forms.[18] VPA may also induce methionine synthase and MTHFR in the liver and can inhibit serine hydroxymethyl-transferase activity, which results in reduced s-FA and increased concentrations of homocysteine.[22,33,37]

The literature on vitamin B12 status in patients treated with AEDs is controversial. Decreased,[35] normal,[22,1] and increased[16,38] s-B12 levels have been reported. In our study, similarly to Apeland et al.[39] and Sener et al.,[14] there was no difference in s-B12 in patients with chronic epilepsy and newly diagnosed epilepsy.

Patients receiving AEDs often develop depressive symptoms,[16,17,19] which are particularly evident in patients treated with phenobarbital, vigabatrin, felbamate, levetiracetam, or topiramate. VPA and CBZ can also cause depressive episodes despite their mood-stabilizing properties, albeit less often. An increased socioeconomic (financial) stress, stressful life events and poor adjustment to seizures have been shown to predict development of depression.[16] Regarding the etiology of interictal depression, the effect of p-tHcy on mood has rarely been discussed in the past decade. But the most important metabolic disturbance in depression is abnormal monoamine (serotonin, dopamine, noradrenaline) metabolism. Clinical and experimental studies link folate, S-adenosylmethionine (SAM) and monoamine metabolism, probably via the bipterin pathway.[19,40] Patients with elevated tHcy had significantly lower concentrations of folate, SAM and monoamine metabolites in central nervous system compared with patients with normal tHcy.[18] Folate deficiency is associated with greater severity of depression and poorer response to standard antidepressant therapy.[21,41] Treatment with folate resulted in improved drive, initiative, alertness, concentration, mood and sociability.[21,42]

Our study has shown no correlation between p-tHcy, s-FA, or s-B12 levels and BDI score regardless of the drug given; however, there was a significant decrease in BDI score in patients with chronic epilepsy after 1 year of supplementation, and an increase in BDI score in patients with newly diagnosed epilepsy after 1 year of VPA or CBZ therapy that was significant only in VPA-treated patients. Rosche et al.[16] observed a significant negative correlation between s-FA levels and scores on the Self-Rating Depression Scale in patients with chronic epilepsy. In large population study from Norway, increased p-tHcy level was associated with increased risk of depression but not anxiety.[17] Hermann et al.[20] and Bottiglieri et al.[19] have described elevated p-tHcy as a sensitive marker of functional folate deficiency, and impaired monoamine neurotransmitter metabolism in patients with depression but without epilepsy. Further studies are needed to elucidate the impact of homocysteine metabolism on interictal depression in patients with chronic epilepsy, although the real pathogenetic role of hyperhomocysteinemia has not yet been clarified.

The risk of resistance to AEDs and development of refractory epilepsy is increased due to homocysteine's convulsant potential.[10,13,43] Several investigators have reported the induction of seizures by the administration of high doses of exogenous homocysteine in experimental models,[12,22,44] but if the blood–brain barrier is damaged locally by trauma or a heat lesion, the dose required for an epileptogenic effect is much lower.[21] If the blood–brain barrier is circumvented by intraventricular or intracortical administration all folate derivatives are highly convulsant as well. It has been also proven that such seizures can be prevented by administering *N*-methyl-D-aspartate (NMDA) or non-NMDA receptor antagonists,[11,12] and recently it has been reported that group II metabotropic glutamate receptor (mGluR) agonists can also prevent seizures.[13,18] In our study there was a significant decrease in seizure frequency in a group of patients with chronic epilepsy after p-tHcy level was decreased with 1 year of vitamin B supplementation. Although the effects of multivitamin supplementation are clear[31] some observations indicate that mild to moderate hyperhomocysteinemia is not necessarily associated with increased seizure frequency in epileptic patients.[14,43] The risk of aggravating epileptic seizures by folate is also small because the blood–brain barrier limits its entry.[21]

Folate and vitamins B6, B2, and B12 are involved in the homocysteine pathway. However, although the effects of food supplementation on p-tHcy levels have been studied, there is no

consensus regarding the dosage of vitamins that should be used to treat hyperhomocysteinemia. In humans, the blood–brain barrier limits the passage of vitamins into the central nervous system, and so excessive supplements should be avoided.[11]

After 1 year of vitamin supplementation in doses mentioned above, p-tHcy significantly decreased only in CBZ-treated patients, s-FA significantly increased in both CBZ- and VPA-treated patients. However, s-B12 significantly increased only in VPA-treated patients. The number of patients with hyperhomocysteinemia decreased significantly. In the study by Apeland et al. patients were supplemented with vitamin B for only 30 days and s-FA increased, while p-tHcy decreased.[30] Clinical trials with long-term follow-up (at least 3 months to 1 year) are needed, as the impact of folate is slow and cumulative over many months.

Adding folate to AED therapy would be easy in everyday clinical practice.[10,13,15,18,45,46] Patients with epilepsy need to be routinely screened for p-tHcy concentrations, especially patients who have been receiving treatment for many years. Inexpensive and safe supplements could be easily taken daily. Supplementation in patients receiving AEDs has a variety of clinical implications: it can affect anticonvulsive efficiency, cardiovascular risk, cognitive performance, and mood.[13,21,31] The Heart Outcomes Prevention Evaluation (HOPE)2[9] study and The Norvegian Vitamin (NORVIT) trial[8] however suggest that treatment with vitamin B have no effect on stroke recurrence or on complications and death from cardiovascular causes. Therefore, homocysteine could be a marker, but not a cause of vascular disease. Although a combination of three vitamins is commonly administered, greater effectiveness has been attributed to folate, which alone (in doses of 0.5 and 5 mg daily) significantly reduces plasma homocysteine levels (25%).[13,15,37] The lowest effective dose of folate for patients taking AEDs still remains to be elucidated. Additionally, folate must be administered continuously, otherwise folate stores would rapidly become depleted, and p-tHcy would increase again.[31,47] For all women with childbearing potential who take AEDs, long-term vitamin therapy may be necessary as prophylaxis against the development of fetal neuronal tube defects.[15,18,23,47]

Our study has some limitations: small sample size, wide age range, patients were not genetically tested, so the influence of polymorphisms affecting folate and Hcy metabolism could not be excluded. Despite these limitations the present study provide novel insights into clinical observations, which can be helpful in the development of new treatment strategies in patients with epilepsy.

5. Conclusions

Homocysteine may contribute to some health problems in patients with epilepsy. Physicians should consider the interactions of AEDs with homocysteine metabolism. VPA or CBZ monotherapy may significantly increase p-tHcy level in patients with epilepsy after just 1 year of treatment. A prospective cohort study should be performed to assess the clinical relevance of our findings: effects of vitamin supplementation on depressive symptoms (Beck Depression Inventory scores) and on seizure frequency. In the future clinical, pharmacological and genetic studies (concerning predisposing genetic factors, such as polymorphisms of folate or vitamin B12 dependent enzymes) may better clarify and quantify whether vitamin supplementation can reduce plasma homocysteine levels in patients treated with AEDs, the way it reduces the risk of CNS development disorders. Neurologists should advise and engage epileptic patients regarding the importance of physical exercise and healthy diet.

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