

# Effects of Common Anti-epileptic Drugs on the Serum Levels of Homocysteine and Folic Acid

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## ABSTRACT

**Objectives:** Elevated total plasma homocysteine has been established as an independent risk factor for CVD. A strong relationship between plasma homocysteine levels and mortality has been reported in patients with CAD. Interference with folate and homocysteine metabolism by some drugs, may lead to increased plasma homocysteine levels. The object of the study was to examine the effect of AEDs on the serum concentrations of folic acid.

**Methods:** A total of 22, older than 18-year-old, epileptic patients, admitted in the Neurology Clinic, who were treated with AED at least for one year were selected. Twenty-two sex- and age-range-matched controls were enrolled in the study. Concentrations of total homocysteine and folic acid in the serum were measured in a fasted status. Demographic and medicine information was collected via a questionnaire. Data were analyzed by spss<sub>16</sub> software.

**Results:** Mean of serum Hcy concentration in the patients was significantly higher compared to that in the controls ( $p = 0.04$ ). Serum folic acid had a nonsignificant negative correlation with the dose of drug used ( $p = 0.2$ ). Serum homocysteine was not significantly correlated with the dose and duration of drug consumption ( $p$  values were 0.4, 0.24, respectively). Serum homocysteine was not significantly correlated with the kind of drug ( $p = 0.4$ ), but folic acid concentration was significantly lower in the monotherapy group than in the poly therapy group ( $p = 0.02$ ).

**Conclusions:** Homocysteine (Hcy) was not different between the epileptic and nonepileptic groups, although the means of the serum folic acid were similar. Possible mechanisms by which AEDs could cause hyper-homocysteinemia might be through the dysfunction of homocysteine metabolism, the acceleration of vitamin metabolism, and the interference in the metabolism of folic acid coenzymes.

**Keywords:** Antiepileptic drug, folic acid, homocysteine

## INTRODUCTION

Homocysteine is an amino acid that is formed by the methylation of methionine. Hcy may get converted to methionine by a reaction that needs 5-methyl THF and B<sub>12</sub> or converted to cystathionin by a reaction that needs PLP.<sup>1</sup>

Many studies suggest that a deficiency of those vitamins that are necessary for Hcy metabolism, is associated with a high concentration of Hcy and low plasma folate.<sup>1,2</sup> Patients who consume antiepileptic drugs are susceptible to high levels of homocysteine and low levels of folate in the blood.<sup>3</sup> High plasma homocysteine has been established as an independent risk factor for cardiovascular disease and thrombosis. A strong relationship between plasma homocysteine levels and mortality has been reported in patients with angiographically confirmed coronary artery disease.<sup>2,4-6</sup> In addition to adverse effects of Hcy on the lipid concentration, it may be a risk factor for cardiovascular events like stroke. Due to the high costs of treating cardiovascular disease<sup>7</sup> and the importance of dyslipidemia in cardiovascular incidence,<sup>8</sup> studies on its predisposing factors are considered to be important.

However, it seems AED therapy is associated with increased Hcy concentration. The data are conflicting about Hcy levels and their relationship with folic acid concentration and AED dosage, so we decided to assess the plasma Hcy and folic acid concentrations in epileptic patients receiving AEDs, to compare them with healthy subjects, and also to assess the patients' status related to the dose and duration of the drug(s) that were used.

## METHODS

In this study, the Case – Control subjects consisted of two groups: The case group consisted of 22 patients, older than 18 years, suffering from epilepsy, who were admitted to the Neurology Clinic and received AED for more than one year (Case group), and the control group consisted of 22 age- and sex-matched persons, who were picked from those accompanying the patients.

Weight was measured, with the subjects in minimum clothes and without shoes, using digital scales and recorded to the nearest 100 g. Height was measured in a standing position,

without shoes, using a tape measure, while the subjects were without shoes and in light clothing and the shoulders were in a relaxed and normal position. Measurements were recorded to the nearest 0.1 cm. Body Mass Index (BMI) was calculated as weight (kg) / height (m<sup>2</sup>).

Information about the demographic characteristics, Familial History of disease, duration of disease, and history of AED use and its dose, were collected via a questionnaire.

Blood samples were taken after overnight fasting. Hcy and folic acid were measured using the Enzyme-linked immunosorbent assay (ELISA), and (Radioimmunoassay) RIA methods, respectively.

For statistical analysis the spss<sub>16</sub> software was used. Results were considered to be significant if  $p < 0.05$ .

All participants provided an informed written consent. This study was approved by the Research Council and the Ethical Committee of the Isfahan University of Medical Sciences.

## RESULTS

In this case – control study 22 epileptic patients on AED and 22 healthy subjects were compared. The means of age, sex, height, weight, and BMI levels are given in Table 1.

The mean of the serum Hcy level showed a significant difference between epileptic and non-epileptic subjects, after adjusting for age, by general linear regression (Table 2).

The serum folate concentration was not significantly different between the case and control groups ( $p = 0.16$ ), after adjusting for age, the relation was weaker ( $p = 0.33$ ).

Near 47.5% of the epileptic patients were using only valproate (VPA) (monotherapy group). Folic acid concentration was significantly lower in them compared to those in the poly therapy group (who received other drugs added to valproate including carbamazepine, Phenobarbital, phenytoin, topiramate, and lamotrigine). The homocysteine concentration was not significantly different between the two groups (Table 3).

**Table 1.** Demographic data of patients and controls

	BMI (kg/m <sup>2</sup> )	Duration (year)	Weight (kg)	Height (cm)	*Age (years)
Control	25.27 ± 1.19 (21)		70.71 ± 3.65 (21)	166 ± 1.94 (22)	28.54 ± 1.52 (22)
Case	23.49 ± 1.25 (18)	4.72 ± 0.93 (18)	67.86 ± 4.64 (18)	167 ± 2.73 (18)	23.00 ± 1.53 (19)
P-value	0.31	-	0.85	0.51	0.01

\* Values in a row are mean ± SEM

**Table 2.** Comparison of homocysteine and folic acid concentrations among epileptic patients and nonepileptic subjects

	Folic acid (n)	Homocysteine (n)
Control	16.12 ± 2.056 (19)	12.97 ± 0.46 (21)
Case	12.52 ± 1.34 (17)	13.66 ± 0.95 (19)
P-value	0.33	0.048

Folic acid concentration had a negatively non-significant correlation with the dose of the drug ( $r = -0.219$ ,  $p = 0.2$ ). Homocysteine showed a positive non-significant correlation with the dose of drug consumption ( $r = 0.009$ ,  $p = 0.48$ ). On the other hand, there was a negative correlation between homocysteine, folic acid, and duration of drug receipt, although it was not significant ( $r$  was  $-0.17$  and  $-0.28$  and  $p$  values were  $0.24$  and  $0.14$ , respectively).

## DISCUSSION

Our findings showed higher Hcy concentration in patients treated with AEDs.

Several studies demonstrated that by treatment with AEDs, the plasma Hcy concentration was elevated.<sup>5</sup> Similar to our study, Sener *et al.* also found that epileptic patients on AED had higher levels of blood homocysteine.<sup>3</sup> In Attilakos *et al.*'s study valproate and carbamazepine significantly increased Hcy when compared to the Control group.<sup>9</sup>

Homocysteine and its oxidative derivative, homocysteic acid, are potentially agonists of the N methyl D aspartate-type glutamate receptor that is linked to epileptogenesis.<sup>3,5</sup>

The mechanism of the association between homocysteine and epilepsy is not fully understood, it is recommended that AEDs increase serum Hcy by decreasing the blood folate levels, due to antifolate properties, and depletion of other vitamins like B2 and B6.<sup>1,3,10</sup>

The folic acid concentration of plasma did not show a significant difference between the two groups. Our result was in accordance with the findings of Schwaninger *et al.* and Sener *et al.*<sup>2,3</sup> On the other hand, AED therapy resulted in increasing homocysteine and decreasing the folic acid levels in Tan *et al.*'s study.<sup>11</sup>

**Table 3.** Comparison of homocysteine and folic acid concentration in epileptic patients according to antiepileptic drug\*\*

Drug	variable	Polytherapy* (n=9)	Valproate(n=10)	p-value
	Homocysteine (pm/l)	13.53 ± 0.68	13.77 ± 1.74	0.4
	Folic acid (ng/d)	15.3 ± 1.54	10.57 ± 1.82	0.02

\* Valproate + other drug(s)

\*\*Values in a row are mean ± SD

In this study, patients who received many antiepileptic drugs (poly therapy) showed a lower concentration of folic acid (Table 3). Folic acid is a cofactor in the methylation of homocysteine and its deficiency is observed in patients with AED treatment such as valproate and phenytoine.<sup>11</sup>

Although whether the mechanism of the AEDs induces folate depletion is not completely clear. It is suggested that there is an interference with intestinal folate absorption, enzyme activity alteration, folate depletion, and finally interference into the metabolism of the coenzyme forms of folate.<sup>1,5</sup>

On the other hand, Hcy concentration is not significantly lower among epileptic patients receiving valproate as compared to poly therapy patients ( $p = 0.4$ ). This is similar to the findings by Shwaning *et al.* and Ono,<sup>2,12</sup> They reported that Hcy concentration is elevated in patients on poly therapy. However, Tamura *et al.* reported that in four groups of patients on AED, any one from the valproate group showed hyperhomocysteinemia.<sup>13</sup>

Gidal *et al.* also did not observe higher plasma Hcy in patients who received Valproate.<sup>12</sup> The effects of VPA are not fully understood, it is suggested that VPA with less enzyme-inducing activity is associated with a small effect on folate depletion and results in increasing the Hcy level.<sup>2</sup>

In our results like in many other studies, the duration of AED treatment positively correlates with homocysteine concentration,<sup>3</sup> however, it is not significant.

In Sener *et al.*'s study, the duration of AED consumption was correlated with folic acid levels, but not with Hcy.<sup>3</sup>

## CONCLUSION

Our data suggest that administration of AED alters the metabolism of Hcy and folic acid. Our contradictions in the insignificant data may be of sample size, on the other hand all the epileptic patients received VPA. Further studies with a larger number of subjects are needed.

- Preventive care in epilepsy is necessary in CVD screening
- Initiation or change of seizure medication may be a future consideration in patients
- Monitoring of serum Hcy in cardiovascular disease patients on AED is necessary
- Treatment with folate or vitamins B6 and B12 lowers plasma homocysteine levels effectively and is relatively inexpensive

It is suggested that similar researches be conducted, with a larger sample size

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