Research Article

Folic acid level and lipid profile in epilepsy patients on antiepileptic drug treatment

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ABSTRACT

Background: Folic acid deficiency occurs in some epileptic patients on long term treatment with enzyme inducing antiepileptic drug (AED) particularly phenytoin and this may lead to the development of atherosclerosis due to the lipid profile alteration.

Objective: The present study was planned to investigate folic acid level and lipid profile among patients with epilepsy on antiepileptic drug treatment.

Materials and Methods: A 25-week, prospective study was conducted in 250 bedded private hospital, Salem, Tamil Nadu, India. In this study, an attempt was made to compare the folic acid level, lipid profile and atherosclerotic risk including Framingham risk score between the normal healthy volunteers (Control), patients with newly diagnosed cases of epilepsy (Supercontrol) and patients with more than one year of antiepileptic drug treatment (Cases).

Results: Folic acid level (in ng/dl) was found to be lower in cases (7.26 ± 2.98) than control (12.69 ± 5.64) and super control (9.35 ± 2.73) - the difference was statistically significant ($p < 0.05$). Normal total cholesterol (TC) level (162.0 ± 23.22 mg/dl) and normal very low density lipoprotein (VLDL) level (40.5 ± 12.89 mg/dl) was observed in cases. But decrease in high density lipoprotein (HDL) level (36.5 ± 12.45 mg/dl), elevated triglycerides (TGs) level (202.5 ± 64.44 mg/dl) was noted in cases and the difference was found to be significant ($p < 0.05$) as compared to control and supercontrol. TC/HDL ratio, LDL/HDL ratio and TG/HDL ratio were increased in cases when compared with control and supercontrol. Framingham risk score reveals slightly higher risk in cases as compared to control and supercontrol.

Conclusion: The result of this study reinforces the results of previous reports in terms of folic acid deficiency with AED treatment and the correlation between folic acid deficiency and cardiovascular risk needs to be established.

Key words: Folic acid, lipid profile, antiepileptic drug, atherosclerosis.

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INTRODUCTION

Epilepsy is a common chronic neurological disorder characterized by seizures.[1] These seizures are transient signs and/or symptoms of abnormal, excessive or hypersynchronous neuronal activity in the brain.[2] In 2007, the incidence rate results from India were higher, and reached 60 per 100000 person/ years. The overall prevalence rate of epilepsy in India is 5.59 per 1,000 populations, with no statistically different rates between men and women or urban and rural residence.[3] The antiepileptic drugs (AEDs) induce the activity of different liver enzymes. This liver enzyme induction may cause depletion of the cofactor folic acid leading to the alterations observed in homocysteine status.

Homocysteine, a sulfur-containing amino acid, is an intermediate of methionine metabolism and its metabolism is regulated by vitamin cofactors, including folate, vitamin B-12, B-6 and B-2.[4] Hepatic cytochrome P450 enzymes are important in cholesterol synthesis. AEDs had been shown to significantly alter homocysteine and lipid profiles in ways that may promote

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arteriosclerosis. Cytochrome P450 enzymes are present in most tissues of the body, and play an important role in hormone synthesis and breakdown (including estrogen and testosterone), cholesterol synthesis and vitamin D metabolism. CYP450 induction should reduce feedback inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase and increase cholesterol. Epilepsy patients treated with carbamazepine or phenytoin for long periods exhibited increased levels of cholesterol and total homocysteine (tHcy) and lower levels of folic acid. All of these may increase risk of adverse cardiovascular and cerebrovascular events.[5,6]

Phenytoin is the first-line anticonvulsive agent and commonly used in epileptic patients because of its broad spectrum of activity and tolerability. It is a drug of first choice for tonic-clonic and partial seizure. Previous studies had reported that increasing duration of phenytoin drug treatment may alter the folic acid level and lipid profile.[6] Controversy still exists about the relationship between folic acid level and lipid profile reported from previous studies. So this study was planned to find out the status of folic acid and lipid profile in patients on phenytoin drug treatment for different duration and to make an attempt to address the issue on the relationship between folic acid level and lipid profile in patients with epilepsy. The present study was conducted in South Indian population where least articles have been published till date on this issue.

MATERIALS AND METHODS

Study design

This prospective study was done at SKS hospital, Salem, India. Data was collected for 6 months between September 2011 to February 2012.

The study was approved by the Institutional Ethics Committee (IEC/Sep/2011/03) of Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode, India. Subjects were included in the study after obtaining informed consent.

Inclusion Criteria

Study subjects (adults 18-50 years of age) were divided into three categories :

Control: Normal healthy volunteers.

Supercontrol: Newly diagnosed epileptic patients.

Cases: Epileptic patients on phenytoin monotherapy for more than one year.

Exclusion Criteria

Patients with other co-morbid conditions, smokers and alcoholics were excluded from the study.

Estimation of folic acid and lipid profile

Folic acid level was determined by electrochemiluminescence immunoassay (ECLIA).[7] Normal folic acid reference is 3.56 - 20 ng/ml.

The serum levels of total cholesterol (TC), high density lipoprotein (HDL) and triglyceride (TG)[8-10] were measured using reagents from Bayer Diagnostics India Ltd, Baroda, India. The values of low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were calculated using Friedewald's equation.[11] The total cholesterol of < 200mg/dl, triglycerides of < 150mg/dl, HDL of > 40mg/dl), LDL of < 100mg/dl, VLDL of < 30 mg/dl were considered as normal lipid profile.

Framingham risk score

Risk score was calculated using risk assessment tool. This tool predicts a person's chance of having a heart attack in the next 10 years.[12]

Statistical Analysis

Differences between the mean ± SD of groups (case, control and supercontrol) were analyzed by using one way ANOVA with Tukey -Kramer multiple comparisons test. 95% confidence interval was used and a p value of < 0.05 was considered as statistically significant. Statistical analysis was made using the Graph pad In stat prism software package.

RESULTS

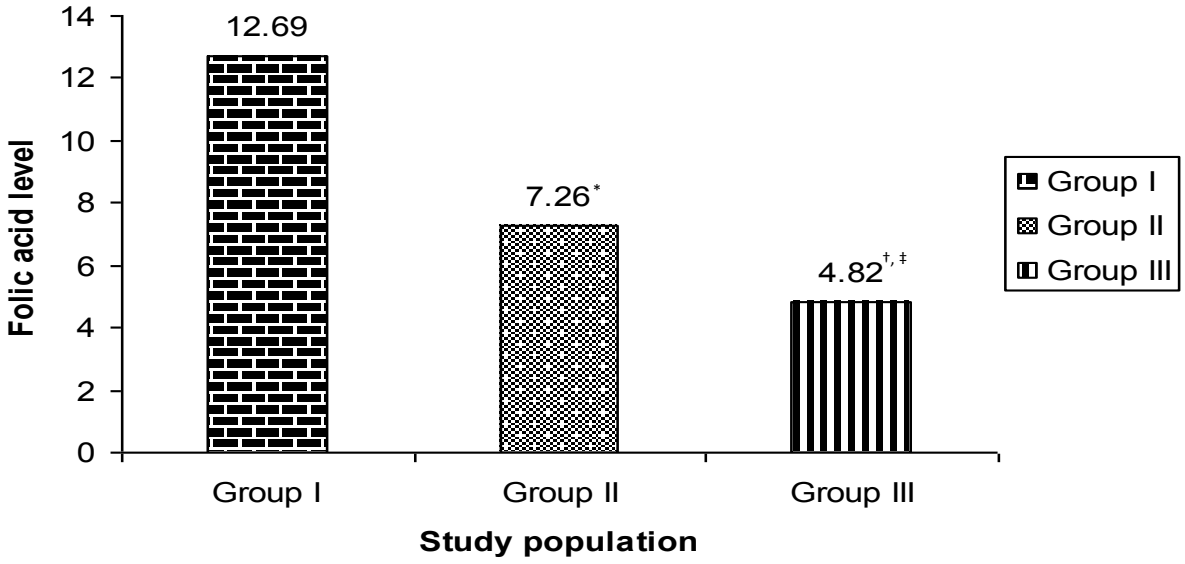
Totally 60 patients (Males - 30 and female - 30) were included as per the inclusion and exclusion criteria. Control, supercontrol and cases consisted each of 20 patients. The statistically significant differences in folic acid levels were observed between control, supercontrol and cases (Figure 1).

Results in Table 1 show that TC, VLDL, LDL/HDL ratio and systolic blood pressure were found to be normal in all the study subjects. LDL level was little higher in control group and the difference was found to be statistically significant with other study groups. According to Framingham risk score, there was no cardiovascular risk among the entire study subjects. But TG/HDL ratio and TC/HDL ratio revealed a borderline risk for cardiovascular events in cases.

A negative correlation was observed between TG levels and HDL levels in all study groups including control (110.18 ± 61.16 and 50.45 ± 9.58), supercontrol (177.41 ± 73.05 and 44.65 ± 5.58) and cases (202.5 ± 64.44 and 36.5 ± 12.45) and the differences between groups were also found to extremely significant. Tukey-kramer multiple comparison also revealed extremely significant difference between supercontrol and cases while comparing TGs and HDL. Low HDL and increase in TGs is a predominant risk factor for cardiovascular complications.

Depletion of folic acid level was directly related with the increasing duration of phenytoin treatment and risk for cardiovascular and cerebrovascular events.

Figure 1: Distribution of folic acid in the study subjects (n=60)



Values are expressed in mean ng/ml.
Group 1- Normal healthy volunteers, Group II - Newly diagnosed epileptic patients,
Group III- Epileptic patients on phenytoin monotherapy for more than one year.
*p < 0.05, group I vs group II; †p < 0.05, group II vs group III ; ‡ p < 0.05, group I vs group III

Table 1: Comparison of folic acid level, lipid profile and Framingham risk score in study subjects

Parameters	Group I (n=20)	Group II (n=20)	Group III (n=20)
Folic acid (ng/dl)	12.69 ± 5.64	9.35 ± 2.73 *	7.26 ± 2.98‡
Total cholesterol (TC) (mg/dl)	184.31 ± 33.33	161.24 ± 15.11*	162.0 ± 23.22‡
High density lipoprotein (HDL) (mg/dl)	50.45 ± 9.58	44.65 ± 5.58*	36.5 ± 12.45†, ‡
Triglyceride (TG) (mg/dl)	110.18 ± 61.16	177.41 ± 73.05*	202.5 ± 64.44†, ‡
Low density lipoprotein (LDL) (mg/dl)	108.0 ± 22.88	96.0 ± 10.30*	97.25 ± 12.64‡
Very low density lipoprotein (VLDL) (mg/dl)	35.44 ± 14.53	22.04 ± 12.23*	40.5 ± 12.89‡
TC/HDL ratio	3.73 ± 0.63	3.66 ± 0.65	4.98 ± 1.76†, ‡
LDL/HDL ratio	2.21 ± 0.51	2.21 ± 0.43*	3.03 ± 1.12†, ‡
TG/HDL ratio	3.64 ± 1.63	2.56 ± 1.51*	5.98 ± 1.80†, ‡
Systolic blood pressure (mm Hg)	120.0 ± 0.00	114.29 ± 10.69*	112.5 ± 8.56‡
Framingham risk ratio	2.0 ± 1.41	2.0 ± 0.85	2.71 ± 2.49

Group 1- Normal healthy volunteers (controls), Group II - Newly diagnosed epileptic patients (supercontrol), Group III- Epileptic patients on phenytoin monotherapy for more than one year (cases).
* $p < 0.05$, group I vs group II, † $p < 0.05$, group II vs III, ‡ $p < 0.05$, group III vs group I

DISCUSSION

It was noted that subjects of control group had higher folic acid level when compared to the other study groups, control and cases. This indicates that phenytoin monotherapy may induce depletion of folic acid. Kishi *et al.*, (1997) suggested that phenytoin, phenobarbitone and carbamazepine, as enzyme inducers, can directly modulate the activity of different liver enzymes[13] leading to depletion of folic acid, elevation of homocysteine (Hcy) level and hyperhomocysteinemia was found be independent risk factor for cardiovascular and cerebrovascular events.[14-16]

In this study, folic acid levels and HDL levels were significantly lower and triglycerides levels were higher in patients on phenytoin monotherapy as compared to other groups. Hence, an increase in duration of phenytoin montherapy might be a risk factor for cardiovascular and cerebrovascular events. Epidemiological studies had shown enhanced risk for heart disease and stroke in persons with epilepsy.[17]

This study indicates the direct relationship between folic acid and HDL levels. Previous studies reported that the increase in HDL following the intake of folic acid and the reduction in LDL.[18-20] The controversy still remain on rationale of using folic acid supplementation in lipid profile alteration.[21,22] This study highlights the relationship between folic acid and HDL and chances for minimizing

atherosclerotic risk in epileptic patients.

The study has its own limitation since baseline investigation of folic acid level and lipid profile among the study groups was not done. The current study is a preliminary attempt to understand the folic acid level and lipid profile among the newly diagnosed epileptic population and AED treated group. There is a need for further longitudinal studies to understand the relation between anti-epileptic therapy with folic acid deficiency and altered lipid profile. Additionally, the effect of folic acid supplementation on the HDL level in epileptic population needs to be established.

The study results showed the link between anti-epileptic drug treatment and folic acid deficiency along with altered lipid profile. These changes might increase the risk of atherosclerosis and cardiovascular disorders. The present study highlights the need for monitoring folic acid level and lipid profile in regular clinical practice in order to reduce the atherosclerotic risk among the epileptic population under AED treatment.

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