ORIGINAL RESEARCH

Evaluation of Efficacy of Folic Acid Supplementation on Homocysteine Levels in Children Taking Antiepileptic Drugs at a Tertiary Care Centre

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Received: 10 January, 2020 Accepted: 22 February, 2020

ABSTRACT
Background: To study the folic acid supplementation on level of homocysteine in children on antiepileptic medication. **Materials & Methods:** A total of 40 participants were included in the study, with 30 assigned to the experimental group and 10 to the control group. Pearson correlation test was employed for assessing correlations, and a significance level of $P < 0.05$ was considered.**Results:** Forty participants were included in the study, and there were no significant differences in baseline data between the two groups. Throughout the follow-up period, no serious adverse reactions were observed.**Conclusion:** The administration of folic acid supplementation in children undergoing antiepileptic drug (AED) treatment may lead to a decrease in total homocysteine (tHcy) levels, potentially mitigating the risk of cardiovascular disease (CVD).
Keywords: Folic Acid, Antiepileptic Drugs, Homocysteine.

INTRODUCTION

Epilepsy is a group of CNS disorders, a chronic medical condition that requires long-term therapy with antiepileptic drugs (AEDs). However, long-term employment of AEDs may lead to the onset of hyperhomocysteinemia. Thiol-containing amino acid homocysteine is an intermediate product formed during methionine metabolism. With age, the average concentration of homocysteine increases and the range of blood homocysteine concentrations within adolescents range from 4.3 µmol/L to 9.9 µmol/L. Blood homocysteine concentration of greater than 10.9 µmol/L is defined as a hyperhomocysteinemia. Elevated blood homocysteine concentrations, however, are associated with an increased risk for cardiovascular disorders (CVDs).[1] Since the epileptic adolescents are bound to consume AEDs for a longer period of time due to their young age, in comparison to adult populations, this warrants an early intervention to abate hyperhomocysteinemia and its potential to induce CVDs.[2]

Hyperhomocysteinemia (HHCY) is emerging an independent predictor of stroke, atherosclerosis, and cardiovascular disease even among children.[3,4] In adults a 5 µmol/L increase in serum homocysteine (tHcy) levels was associated with an increased risk of stroke and ischemic heart disease by >50% and 30%, respectively. [5] Folate status is one of the most important determinants of tHcy concentrations and folic acid supplementation significantly and safely improves homocysteine levels.[6] Folic acid supplements are well tolerated and have been found to decrease homocysteine levels and also to improve vascular function in children.[7] Even a weekly single dose may be beneficial of increasing red blood cell folate levels and

reducing serum tHcy levels.[8] Folic acid deficiency is associated with elevated levels of homocysteine, and this phenomenon appears to be prominent in those receiving enzyme-inducing AEDs.[9,10] Homocysteine levels are elevated both at fasting and after methionine loading in persons receiving CBZ, PHT, phenobarbital (PB), and primidone (PRM).[11] Adults receiving VPA, an inhibitor of cytochrome P450 enzymes, had lower homocysteine levels fasting and after methionine loading than did controls, although children on VPA had low folic acid and elevated homocysteine levels.[12] 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.[13] Hyperhomocysteinemia is associated with vascular disease, including cerebrovascular disease, and may also be associated with neurodegenerative disease. Supplementation with folic acid, vitamin B6 (pyridoxine hydrochloride), and vitamin B12 (cyanocobalamin) readily normalizes homocysteine levels.[14] Hence, this study was conducted to study the folic acid supplementation on level of homocysteine in children on antiepileptic medication.

MATERIALS & METHODS

A total of 40 participants were included in the study, with 30 assigned to the experimental group and 10 to the control group. Baseline data collection and measurement of total homocysteine (tHcy) levels were conducted. The experimental group received 1 mg folic acid tablets, while the control group received placebo tablets for a duration of 30 days. After a one-month follow-up, tHcy levels were reassessed. Statistical significance was evaluated using the $\chi(2)$ test, paired and unpaired t-tests as applicable. Pearson correlation test was employed for assessing correlations, and a significance level of $P < 0.05$ was considered.

RESULTS

Forty participants were included in the study, and there were no significant differences in baseline data between the two groups. Throughout the follow-up period, no serious adverse reactions were observed. The mean post-total homocysteine (tHcy) concentrations were 8.59 for the experimental group and 15.80 micromol/l for the control group. Additionally, pre-tHcy values in both groups did not exhibit a significant positive correlation with the duration of treatment with antiepileptic drugs (AEDs).

Table 1: General parameters

Variables	Mean		P value
	Control group (n=10)	Experimental group (n=30)	
Male: female	4:6	18:12	0.22
Age (years)	7.53	8.42	0.52
Age at first episode seizure (years)	2.15	2.87	0.35
Treatment for years	2.87	3.60	0.25
Current AED drugs	Number	Number	
Phenytoin	1	5	0.25
Phenobarbitone	0	8	0.045

Table 2: Homocysteine values

Variables	Mean		P value
	Control group	Experimental group	
Pre-tHcy (micromole/l)	14.05	12.78	0.5
Post-tHcy (micromole/l)	15.80	8.59	0.006**
Prevalence of decrease	Number (%)	Number (%)	
Post -tHcy values	2	18	0.003**

**P<0.01

DISCUSSION

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.[15] Although that concern is no longer held by epileptologists, the dosage restriction persists. Hence, this study was conducted to study the folic acid supplementation on level of homocysteine in children on antiepileptic medication.

In the present study, forty participants were included in the study, and there were no significant differences in baseline data between the two groups. Throughout the follow-up period, no serious adverse reactions were observed. A study by Cherumanalil et al, assessed the level of homocysteine (tHcy) in children taking AEDs and to study whether daily oral supplementation of folic acid for 1 month will reduce the tHcy level. This was a double-blinded, randomized control trial conducted in Institute of Maternal and Child Health, Kozhikode, India. Totally 60 children were recruited and of them, 48 were enrolled. Of these children, 32 were assigned to the experimental group and 16 to the control group. Baseline data collection and tHcy estimation were done. One mg folic acid tablets were given to the experimental group and placebo tablets to the control group for 30 days. tHcy levels were re-estimated after 1 month follow-up. Baseline plasma tHcy concentrations in both groups were comparable [11.90 (6.3) and 13.02 (2.4) μmol/l, respectively]. During the follow-up period, no increase in seizure episodes or no serious adverse reactions were noticed in either group. The reduction of tHcy in the experimental group was 1.92 μmol/l ($P = 0.04$) and in the control group, there was an increase of 1.05 μmol/l ($P = 0.16$). In children on AED treatment, folic acid supplementation may reduce tHcy level and thus reduce CVD risk.[16]

In the present study, the mean post-total homocysteine (tHcy) concentrations were 8.59 for the experimental group and 15.80 micromol/l for the control group. Additionally, pre-tHcy values in both groups did not exhibit a significant positive correlation with the duration of treatment with antiepileptic drugs (AEDs). Another study by Papandreou D et al, five hundred and twenty-four children participated in

the study; Twenty six of them were found to be hyperhomocysteinemic (>95th percentile for age). Twenty of them received 5 mg of folic acid twice per week for two consecutive months while the other six received a diet rich in dietary folate. Serum homocysteine levels were statistically significantly decreased from 13.1 (10-24.2 µmol/L) to 7.7 (4.9- 15.2 µmol/L), p<0.001. Serum folate levels were significantly rose from 4.3 (3-20 ng/mL) to 16.8 (7-20 ng/mL), p<0.001. On the contrary, no important changes were observed in the above parameters in children to whom a diet rich in folic acid were recommended. Homocysteine levels were found to be positively associated with age (r=0.314, p<0.001), BMI (r=0.192, p<0.001), WC (r = 0.215, p<0.001), simple sugars (r= 0.182, p<0.001) and negatively associated with folic acid (r = -0.331, p<0.001), vitamin B12 (r = -0.214, p<0.001) and dietary folic acid (r= -0.228, p=0.003). Oral folic acid 5 mg twice per week may efficiently reduce serum homocysteine levels and increase serum folic acid levels in healthy children with increased homocysteine levels (>95th percentile for age). Hyperhomocysteinemia in childhood may be a predictive factor of cardiovascular disease. In addition, these results may offer more help to health practitioners in order to establish more prospective studies to elucidate the relationship between homocysteine, folic acid and heart disease in children.[16] Bhosale UA et al, designed to explore the effects of folic acid (FA) supplementation on AED-induced hyperhomocysteinemia and CVD risk factors in adolescent epileptics. The randomized clinical trial included adolescent epileptics (i.e., 10-19 years of age) of either sex, on antiepileptic therapy for > 6 months with high homocysteine levels (i.e., >10.9 µmol/L). At the time of enrolment, their baseline BP, lipid and homocysteine levels were recorded. Participants were randomly assigned to either treatment or placebo groups and received the respective treatments. At the end of the first month, BP, lipid and homocysteine levels were recorded and compared to determine the effect of FA on these parameters. A significant fall in homocysteine levels was observed with FA supplementation (P < 0.05). However, this fall was significantly high in valproic acid treated epileptic patients. In addition, we observed an improvement in high-density lipoprotein levels, a risk factor for CVDs, but the change was statistically insignificant (P > 0.05). The study results suggest that FA supplementation in epileptic patients receiving AED therapy may minimize AED-induced hyperhomocysteinemia and other CVD risk factors.[17] Huemer M et al, assess the prevalence of hyperhomocysteinemia in pediatric patients treated with antiepileptic drugs (AEDs) and to evaluate the effect of folic acid supplementation on plasma total homocysteine (tHcy) concentrations in hyperhomocysteinemic patients. 123 patients from three regional hospitals participated in the study. Patients with hyperhomocysteinemia were included in a 3-month double-blind randomized trial testing oral folic acid supplementation (1 mg/day) versus placebo. Hyperhomocysteinemia (tHcy>10.4 micromol/L) was present in 19 of 123 patients. Patients with hyperhomocysteinemia were older (13.7 +/- 4 vs. 11.0 +/- 3.9 years) and had significantly lower folate and cobalamin concentrations. Multidrug (two or more) AED treatment and duration of therapy correlated significantly with elevated total homocysteine (tHcy) and low folate. In contrast, polymorphisms in the methylene tetrahydrofolate reductase gene (MTHFR 677 C-->T, 1298 A-->C, 1793 G-->A) had no significant impact on tHcy. Nine of 19 patients with hyperhomocysteinemia were randomized to placebo, whereas the remaining 10 patients received folic acid supplementation. Folic acid supplementation resulted in a significant increase of folate and decrease of tHcy, whereas both parameters remained unchanged in the placebo group. Hyperhomocysteinemia is present in 15.5% of children receiving long-term AED treatment. Multidrug treatment and long duration of therapy enhance the risk for hyperhomocysteinemia. Folic acid supplementation significantly reduces tHcy.[18] Kurul S et al, investigated the homocysteine, folic acid, and vitamin B(12) levels in epileptic children receiving antiepileptic drugs. A total of 25 children with idiopathic epilepsy (8 valproate, 11 carbamazepine, and 6 oxcarbazepine) and 10 healthy children were included in the study. The mean homocysteine, folic acid, and vitamin B(12) levels in the study group were 7.57 +/- 3.78 micromol/L (normal = 5-15 micromol/L), 10.19 +/- 4.05 ng/mL (normal = 3.0-17 ng/mL), and 428.20 +/- 256.12 pg/mL (normal = 193-983 pg/mL), respectively. The differences between the mean plasma homocysteine, folic acid, and vitamin B(12) levels of the study and control groups were not significant (P = .522; P = .855; P = .798, respectively). However, plasma homocysteine levels were higher than the normal cutoff point accepted for childhood in 4 (16%) of the study patients. Out of these 4 children, 3 were from the carbamazepine group and 1 was from the valproate group. Although the number of the study patients is limited, the authors recommended assessment of plasma homocysteine, serum vitamin B(12), and folic acid levels in children receiving enzyme-inducing antiepileptic drugs.[19]

CONCLUSION

The administration of folic acid supplementation in children undergoing antiepileptic drug (AED) treatment may lead to a decrease in total homocysteine (tHcy) levels, potentially mitigating the risk of cardiovascular disease (CVD).

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