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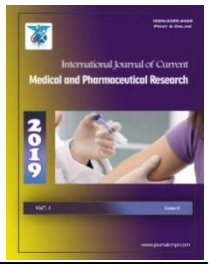

ESTIMATION OF SERUM FOLIC ACID LEVELS IN EPILEPTIC PATIENTS TAKING ANTICONVULSANT DRUGS

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ABSTRACT

Among many deleterious effects of anticonvulsant drugs, depletion of serum folic acid levels is a major one. Serum folic acid levels in epileptic patients taking anticonvulsant drugs were measured in gender matched control subjects without anaemia and outpatients who were epileptic and taking anticonvulsant drugs. Mostly the drugs administered were enzyme inducers or non-enzyme inducers. Compared with the mean serum folic acid levels in control (7.73 +- 2.62 ng/ml: n=30), the mean serum folic acid levels in epileptic patients (5.74 +- 1.9 ng/ml: n=30),were significantly reduced. Findings also showed that reduced serum folic acid levels were significantly found (66.7 %) in anticonvulsant drug induced gingival enlargement patients. The study, though could not establish any relationship between subnormal folic acid levels with age, gender, dose, duration or types (enzyme or non enzyme inducer) drugs.

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures of cerebral origin, with episodes of sensory, motor or autonomic manifestation with or without loss of consciousness. Despite the tremendous advances in the management of epilepsy phenytoin remains the drug of choice particularly in many developing countries. However, long term administration of phenytoin has a number term administration of phenytoin has a number of adverse effects, one of which is lower serum folic acid levels.[1]

The beneficial effect of anticonvulsant drug therapy on control of epilepsy is accompanied by decreased levels of folic acid in many patients. A diversity of mechanisms have been proposed such as induction of liver enzymes (Maxwell *et al* 1972), impairment of folate absorption (Ibbotson *et al* 1967) & a competitive interaction between folate co-enzyme & drugs (girdwood & lenman 1969) by which anticonvulsant drugs may persuade folic acid depletion. Despite of these proposed mechanisms none of them have been confirmed and are still considered to be controversial.[2,3]

A deleterious side effect of low level of serum folic acid level is gingival hyperplasia.[9,10]

Though numerous studies on gingival overgrowth have been conducted such as : association between factors relating to dental hygiene (Seymour 1993), host genetic predisposition (hassell *et al* 1976), multiple antiepileptic therapy (greenwood *et al* 1986) & reduced serum folic acid levels (vogel 1977).Yet, the exact pathophysiology remains uncertain.[9-14,]

The present study was conducted to estimate the serum folic acid levels in epileptic patients taking anticonvulsant drugs. This study also plans to evaluate serum folic acid levels in anticonvulsant drug induced gingival hyperplasia, the effect of duration of anticonvulasant drugs on serum folic acid levelss, effect of different types of anticonvulsant drug therapy on serum folic acid levels and effect of different doses of anticonvulsant drug therapy on serum folic acid levels.

Study Design

Study group (30, epileptic patients) and Control group (30, healthy patients) were selected for the estimation of serum folic acid levels. The diagnosis of epilepsy was based on the clinical symptoms, previous medical records and an undergoing anticonvulsant drug therapy. A thorough case history & oral examinations were performed in all the patients. Gingival enlargement & Oral hygiene were graded according to GO index & Oral hygiene index- simplified respectively. Venous blood was drawn for estimation of serum folic acid levels. Only epileptic patients treated with anticonvulsant drug therapy from last 1-15 yrs are included. The patients' age ranges from 13-45 yr . Patients who were having systemic disorders known to affect the gums, on multivitamin, any other drug therapy, physiological or systemic conditions known to cause folic acid deficiency were excluded from the study. Patients taking anticonvulsive drugs due to any disease, other

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than epilepsy or who have changed their doses in last 1 month prior to study, were also excluded from study. All subjects were selected from the outpatient department of Kothiwal Dental College and Research Centre. (Moradabad , North India)

RESULTS

Table 1 Groupwise Distribution of Subjects

SN	Group	Description	No. of subjects	Percentage
1.	Control	Normal healthy subjects	30	50
2.	Cases	Epileptic subjects on anticonvulsants	30	50

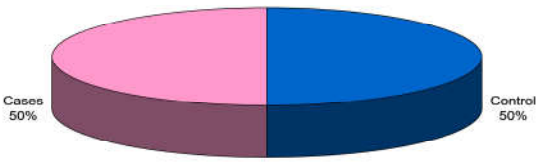


Table 2 Distribution of subjects according to Category of Folic Acid levels

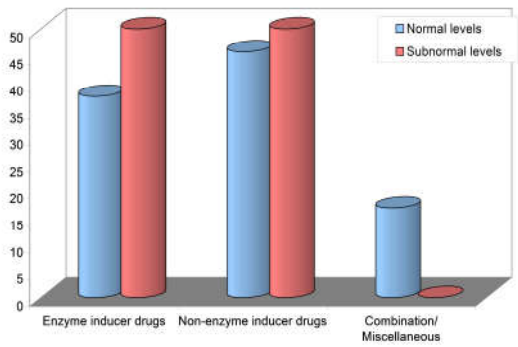
SN	Category	Control (n=30)		Cases (n=30)	
		No.	%	No.	%
1.	Subnormal (<4 ng/ml)	0	0.0	6	20.0
2.	Normal (4-16 ng/ml)	29	96.7	24	80.0
3.	Above normal (>16 ng/ml)	1	3.3	0	0.0

On comparing the data statistically**, a significant difference** was observed between two groups.

Table 3 Association between Folic Acid levels and types of drugs among cases

SN	Types of Drugs	Normal Level (n=24)		Subnormal Level (n=6)	
		No.	%	No.	%
1.	Enzyme inducer drugs	9	37.5	3	50.0
2.	Non-enzyme inducer drugs	11	45.8	3	50.0
3.	Combination/ Miscellaneous	4	16.7	0	0

On comparing the data statistically**, no significant** association between type of drug and serum folic acid category could be seen.

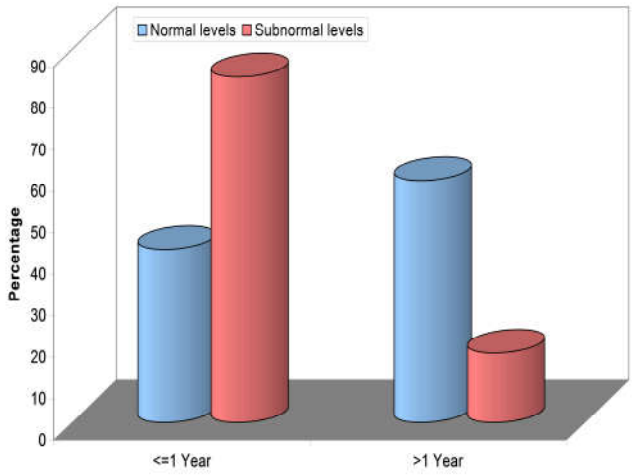


On comparing the data statistically, no significant association between type of drug and serum folic acid category could be seen (p=0.547).

Table 4 Association between Folic Acid levels and duration of drug use among cases

SN	Duration of drug use	Normal Level (n=24)		Subnormal Level (n=6)	
		No.	%	No.	%
1.	≤1 Year	10	41.7	5	83.3
2.	>1 Year	14	58.3	1	16.7

On comparing the data statistically, **no significant** association between period of drug use and incidence of subnormal folic acid levels was observed.

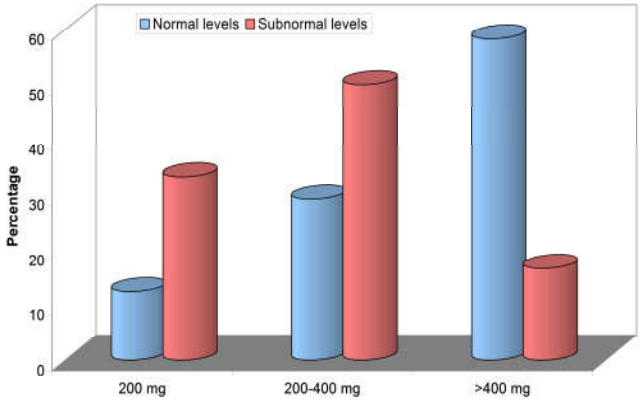


On comparing the data statistically, **no significant** association was found.(p=0.168)

Table 5 Association between Folic Acid levels and dose of drug use among cases

SN	Dose of Drug used	Normal Level (n=24)		Subnormal Level (n=6)	
		No.	%	No.	%
1.	200 mg	3	12.5	2	33.3
2.	200-400 mg	7	29.2	3	50.0
3.	>400 mg	14	58.3	1	16.7

On comparing the data statistically, **no significant** association was found.

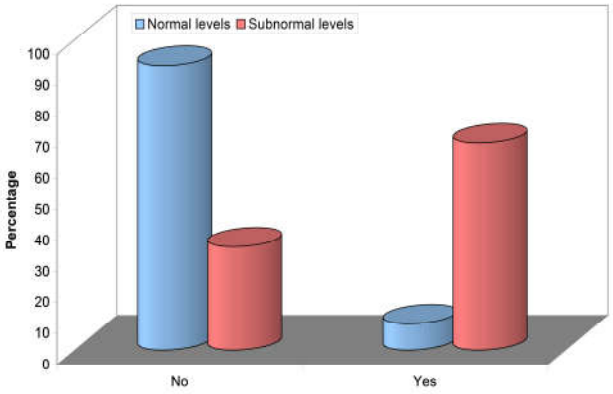


On comparing the data statistically, the association was not found to be significant (p=0.170).

Table 6 Association between Folic Acid levels and gingival hyperplasia among cases

SN	Gingival Hyperplasia	Normal Level (n=24)		Subnormal Level (n=6)	
		No.	%	No.	%
1.	No	22	91.7	2	33.3
2.	Yes	2	8.3	4	66.7

The incidence of gingival hyperplasia was significantly higher among those with subnormal folic acid level



The incidence of gingival hyperplasia was significantly higher among those with subnormal folic acid levels (p=0.001)

DISCUSSION

Several studies was done in the past which confirmed abnormal serum folic acid levels in epileptic patients (Jensen and Olesen, 1969; Reynolds, 1973) receiving anticonvulsant drugs.[2-5] In our study also confirms this fact and found that mean Serum folic acid levels in control group were observed to be 7.73±2.62, which were significantly higher as compared to those among study group which was found to be 5.74±1.90, with 20% 0f epileptic patients having abnormal folic acid levels.

In the preceding studies Klipstein reported abnormal folic acid levels in 58% of epileptic patients, Miller reported abnormal folic acid levels in 52.1% of epileptic patients, Malpas noted abnormal folic acid levels in 37% of epileptic patients. In our study, the conspicuous feature is the decrease incidence of abnormal folic acid levels (20%). The postulation include poor social economic status associated with epilepsy as well as poor nutrition leading to low serum folate levels obtained in this set patient and large sample size than our study.

Few reports have compared the folate depletion among various antiepileptic drugs. Goggin *et al*. showed that folate levels were reduced significantly in patients treated with phenytoin or Carbamazepine (CBZ). However, treated patient with Valproic sodium (VPA), there was no significant decrease in folate levels compared to controls. They suggest that liver enzyme induction is responsible for the low serum folate levels in patients treated with antiepileptic drugs. Phenobarbitone (PB) and CBZ each persuade hepatic microsomal enzymes, whereas VPA and Zonisamide (ZNS) do not (Perucca *et al*., 1984; Konishi *et al*., 1990). Kishi Takamasa *et al* found that the enzyme-inducing antiepileptic drugs reduced the serum folate levels, while the non-enzyme-inducing drugs did not.[16,17] Our study tracking the mean serum folic acid levels between the enzyme and non enzyme drug user subjects. Also, no significant difference was found in the incidence of abnormal folic acid levels in enzyme inducers group (50%) and non enzyme inducers group (50%).In our previous study showed different results, probably because most of our patients taking non enzyme drug group were on valproic sodium (VPA) and there have been dispute reports regarding VPA (Morrel 2002 & Kishi Takamas). A smaller size of our study group could also attribute to this difference.

Several studies have accepted that serum folate levels are below normal in epileptic patients who are receiving long-term treatment with antiepileptic drugs (Klipstein,1964, Kishi 1997), where as some investigators failed to find a correlation between duration of treatment (Malpas *et al*., 1966; Denis *et al* 1967) and serum folic acid levels.[4,8,17]. View of the result of our, Serum folate levels appeared to rise with an increase in the duration of treatment though the results was not significant statistically. Mean Serum folic acid levels appeared to rise with the duration of treatment which could be explained by following two reasons. As the duration increases patient becomes more negligent so misses their daily dose & possible previous treatment with multivitamin.

According to many authors depletion of serum folic acid levels occurs in a dose-dependent manner (Reynolds *et al*., 1971)[17]. Some investigators have failed to find a correlation between folate levels and drug dosage (Malpas *et al*., 1966; Korczyn *et al*., 1974,)[8.] Unlike their study our study founded an increase of mean serum folic acid levels which occurred in the dose dependent manner though it was not statistically significant. It could be due to smaller sample size in our study also further studies with large sample size need to be conducted to establish any fact.

Along with the abnormal folic acid level, gingival hyperplasia has also been recognized as deleterious side effects of prolonged anticonvulsant drug therapy[9-15]. Gingival hyperplasia caused due to reduced serum folic acid levels, Vogels theory is widely accepted. Our studies also confirms Vogels theory that reduced serum folic acid levels is directly related to anticonvulsive drug induced gingival hyperplasia. Majority of antiepileptic drug induced (AED) gingival hyperplasia (66.7%) patients had reduced serum folic acid levels. Those patients who did not have gingival hyperplasia (33.3%), but their serum folic acid level was found abnormal, probably because these patients belonged to the educated society so maintained good oral hygiene.

CONCLUSION

In our study we found that there is significant reduction of mean serum folic acid levels in epileptic patients taking anticonvulsant drugs. The reduced serum folic acid levels has a direct co-relation with anticonvulsive drug induced gingival hyperplasia, but significant relationship between subnormal folic acid levels with the dose of drugs, duration of drugs, type of drugs of epileptic patients could not be established.

References

1. Morrell.M.J: Folic Acid and Epilepsy, Epilepsy Curr. 2002 March; 2(2): 31–34.
2. Maxwell J.D, Hunter J, Stewart D.A, Ardeman S, Williams R: Folate Deficiency after Anticonvulsant Drugs: An Effect of Hepatic Enzyme Induction?, British Medical Journal, 1972, 1, 297-299.
3. Neil gordan: Folic acid deficiency from anticonvulsant therapy. Develop.med.child neurol.1968,10,497-504.

4. Denis r miller: Serum folate deficiency in children receiving anticonvulsant therapy. Pediatrics. vol 41 , no. 3, 1968.
5. Spray G.H, Burns D.G: Folate Deficiency and Anticonvulsant Drugs, *British Medical Journal*, 15 April 1972.
6. Reynolds. E. H: Iatrogenic nutritional effects of anticonvulsants, Proc. Nutr. Sac. (1974),33, 225.
7. Livanainen Matti ' and Savolainen Heikki : Side effects of Phenobarbital and phenytoin during long-term treatment of epilepsy. Current therapy in epilepsy Acta Neurol Scand 1983:68: Suppl97:49-67.
8. Malpas, J.S., Spray, G.H., Witts, L.J: Serum folic-acid and vitamin Bl2 levels in anticunvulsant therapy, Br. Med. J. 1966, 1: 955-961.
9. Vogel R: Gingival hyperplasia and folic acid deficiency from anticonvulsive drugs. A theoretical relationship. J theoretical biology ,1977, 67
10. Gulati. Arya R: phenytoin – induced gingival overgrowth. Acta neurologica, 2011, 1600 – 0404.
11. Ranganathan Lakshmi Narasimhan, *Sridharan Ramaratnam: Folic Acid Supplementation For Epilepsy- A Systematic Review. Neurology Asia 2004; 9 (Supplement 1): 121.
12. WZW.Yus of: Gingival hyperplasia: an intra oral side effect of phenytoin, nifedipine and cyclosporine therapies. SING MED.J.198;29;498-503
13. J.Talan: Folic Acid Supplements in Children with Epilepsy Found to Reduce Gingival Overgrowth, Neurology Today ,April 21, 2011
14. Correa Joice Dias, Queiroz – Junior CM, Costa JE, Teixeira AL, Silva TA: Phenytoin – Induced Gingival Overgrowth: A Review of the Molecular, Immune, and Inflammatory features. ISRN, vol 2011.
15. Labadarios D, Dickerson J.W.T & Parke D.V, Lucas Eg, Obuwa G.H: The effects of chronic drug administration on hepatic enzyme induction and folate metabolism. Br .J.clin.pharmac,(1978), 5,167-173
16. Prasad V N, Chawla H S, Goyal A, Gauba K, Singhi P: Folic Acid and Phenytoin Induced Gingival Overgrowth - Is There A Preventive Effect, J Indian Soc Pedo Prev Dent, June (2004) 22 (2) 82-91.
17. Takamasa kishi *et al*: Mechanism for reduction of serum folate by antiepileptic drugs during prolonged therapy. *Journal of the neurological sciences* 145, 1997, 109 -112.

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