

A Study on Gingival Enlargement and Serum Folic Acid Levels in Epileptic Patients on Phenytoin Therapy

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Abstract – Background - Chronic administration of phenytoin has been associated to have a number of adverse effects. Gingival enlargement is one such most often reported adverse drug sequela of long term phenytoin usage with falling serum folic acid levels seen with increase in the duration of phenytoin therapy. There have been studies that report clinical benefits of the use of folic acid as an adjuvant to the anti-epileptic therapy in the prevention of anti-epileptic drug induced gingival enlargement. However, studies conducted in the past have also reported precipitation of epileptic attacks in patients on folic acid adjuvant therapy due to fall in sera levels of phenytoin due to drug interactions. Hence, the study was planned to investigate the association of phenytoin induced gingival enlargement and sera levels of folic acid in epileptic patients on phenytoin therapy. 25 patients between the ages of 18-50 years clinically diagnosed with epilepsy prior to the start of phenytoin therapy were included based on selection criteria and written informed consents were obtained. Assessment of serum folic acid levels and gingival enlargement was done prior to the start of and after 6 months of phenytoin therapy. The results of the study confirmed a significant association between low serum folate levels and increasing severity of phenytoin induced gingival enlargement. The results of the study suggest a higher incidence of gingival enlargement in phenytoin treated epileptic patients with a positive correlation with falling serum folic acid levels as the duration of the therapy increases.

Keywords – Epilepsy; gingival enlargement; folic acid; phenytoin.

1. Introduction

Epilepsy is described as a chronic neurological disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness [1]. A recent meta-analysis of published and unpublished studies puts an overall prevalence rate of epilepsy in India at 5.59 per 1,000 populations [2].

Despite the tremendous advances in the management of epilepsy, phenytoin still remains the drug of choice; however, the long term administration of phenytoin has been seen to lead to a number of adverse effects. Gingival enlargement is one such most frequently reported adverse effect of phenytoin [3]. Approximately 40-50% of the patients treated with phenytoin develop esthetically disfiguring enlargement of the gingivae. Whenever occurs, this adverse effect of phenytoin, lasts throughout the period of therapy and continues further with a severe reduction in the quality of life of the affected individual. The pseudopockets that are formed as a result of gingival enlargement increase plaque retentive areas which further predispose the patient towards an enhanced susceptibility for inflammatory changes in the gingivae, dental caries and periodontal diseases [4, 5].

The etio-pathogenesis of phenytoin induced gingival enlargement is still not clearly understood, however, many studies indicate its multi-factorial etiology [6], including oral hygiene status of the affected epileptic patients. It has also been seen that phenytoin is not only responsible for the initiation of the enlargement of the gingival tissue but has

also been noted to interfere with folic acid metabolism and especially, absorption thereby leading to a significant decrease in the plasma as well as the tissue levels of the folates [7].

It is being speculated that phenytoin induced end-organ folic acid deficiency conditions the gingival tissues to inflammation by causing degenerative changes in the gingival sulcular epithelium [5], the main physical barrier against local irritants [7]. It is also reported that folic acid interferes with the production of, 5-p-hydroxyphenyl, 5-phenyl hydantoin, [p-HPPH], a major metabolite of phenytoin metabolism, held responsible for gingival enlargement owing to its alkaline nature thereby resulting in gingival enlargement in cases which are associated with folic acid deficiency [8].

On the other hand, folates administered at pharmacological doses have been blamed for a decrease in the serum concentration of phenytoin which is severe enough to precipitate seizures. So, the use of folates as an adjuvant to the anti-epileptic therapy in the prevention of gingival enlargement mandates further clinical and laboratory evaluation.

Based on the conclusions drawn from the various studies correlating decreased plasma and tissue folate levels with phenytoin induced gingival enlargement, folic acid has been tried, both topically and systemically, to prevent this inevitable adverse effect of long term phenytoin therapy, though with varying results [8]. There has been, however, a consistent void in research in assessing serum folic acid levels in epileptic patients and their correlation with the onset

and severity of phenytoin induced gingival enlargement starting from the beginning of phenytoin treatment. Hence, the present study was designed to investigate the association of phenytoin induced gingival enlargement with serum folate levels in phenytoin treated epileptic patients.

2. Objectives of the Study

1. To study the incidence and assess the scores of gingival enlargement in epileptic patients before and after 6 months of phenytoin therapy.
2. To assess serum folic acid levels in epileptic patients before and after 6 months of phenytoin therapy.
3. To correlate the scores of gingival enlargement with serum folic acid levels in patients on phenytoin therapy.

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3. Materials and Methods

3.1. Source of Data

25 patients visiting the Department of Neurology, Victoria Hospital Bangalore during the period of Jan 2009 to Dec 2009 clinically diagnosed with epilepsy were selected prior to the start of phenytoin therapy based on the defined inclusion and exclusion criteria.

3.2. Method of collection of Data

Selected epileptic patients, clinically diagnosed with epilepsy, were explained in detail about the planned study and written informed consents were obtained. These patients were subjected to a detailed history and a thorough clinical examination using a specially prepared proforma.

3.3. Inclusion criteria

1. Epileptic patients in the age group of 18-50 years.
2. Patients who were being started with phenytoin therapy.
3. Patients with full complement of teeth without any carious or periodontal involvement or any other pathological process in the teeth and the jaws.

3.4. Exclusion criteria

1. Epileptic patients with other systemic diseases.
2. Epileptic patients with pre-existing gingival enlargements due to any reasons as idiopathic, inflammatory, neoplastic, endocrinal, chronic vitamin C deficiency, mouth breathing or pregnancy.
3. Epileptic patients on any type of pharmacologic therapy including multi-vitamins or, folate antagonists.
4. Epileptic patients who had history of dental treatment and trauma to teeth.

3.5. Methodology

Based on the selection criteria, 25 patients clinically diagnosed with epilepsy, were enrolled in the study with their written informed consents and then subjected to a thorough oral prophylaxis, routine hematological examination and serum folic acid level assessment. Before the start of study, the ethical clearance was obtained by the ethical committee of the institution as well as from Bangalore Medical College and Research Institute and Associated Hospitals.

3.6. Assessment of serum folic acid

Assessment of serum folic acid level was done by chemiluminiscent method (Figure 1), using Immulite kit (Figure 2) prior to the start of phenytoin therapy. For this, following an overnight fasting period, 5 ml of venous blood was taken from patients from the antecubital vein using a sterile disposable syringe in the sitting position between 8 A.M. and 10 A.M. Serum was immediately separated (Figure3) by ultracentrifugation. The supernatant was discarded (Figure 4) and the rest of the sample was stored at -20 degrees Celsius. (Figure 5) The Flurometer was set at 370 nm excitation with emission monitored at 470 nm. Flow rate was adjusted as 1.3 ml/min. (Figure 6)

After a gap of one week, these patients were thoroughly examined and their gingival status assessed using the index originally described by ANGELOPOULOS and GOAZ and later, modified by MILLER AND DAMM [GO INDEX]. (Figure 7)



Figure1. Equipment for assessment of serum folic acid levels



Figure2. Immulite 1000 folic acid chemiluminiscent immunoassay kit with sera samples.



Figure 3. Serum component separated from the blood sample.



Figure 4. Microtitre pipettes with pipette tips



Figure 5. Stored serum samples in plastic vials.

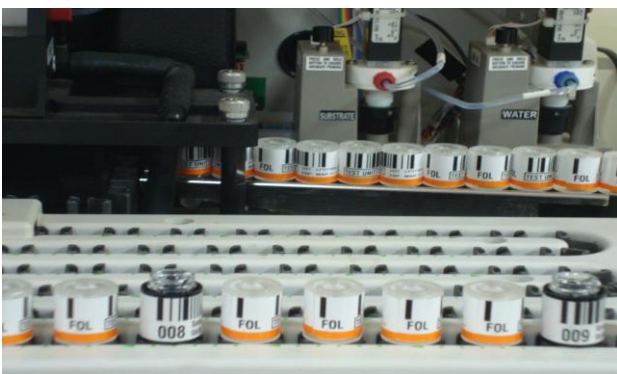


Figure 6. Equipment for assessment of serum folic acid levels by chemiluminiscent immunoassay system with running samples.



Figure 7. Clinical picture of gingival status in a male epileptic patient before the start of phenytoin therapy, after 1 week of oral prophylaxis.



Figure 8. Clinical picture of gingival enlargement in a male epileptic patient (GRADE 1) after 2 months of initiation of phenytoin therapy.



Figure 9. Clinical picture of gingival enlargement in a male epileptic patient (GRADE 2) after 6 months of phenytoin therapy.



Figure 10. Clinical picture of bulbous gingival enlargement in a female epileptic patient with more prominent involvement of the interdental papillae (GRADE 3) after 6 months of phenytoin therapy.

Assessment of gingival enlargement: The gingival status was assessed using the [GO INDEX]. The height of gingival tissue was measured from the cemento-enamel junction to the free gingival margin. The grades for gingival enlargement were assessed in relation to the six anterior teeth in both the maxillary and mandibular arches based on the findings of the previous studies of the more common involvement of the anterior segments of the jaws, both on the mesial and the distal inter-proximal aspects and the greater score amongst them was selected to be included to refer to the peak effect of the drug.

After a period of 2 months, the patients were reviewed and their gingival scores re-assessed (Figure 8) using the same criteria. The same procedure was repeated at the end of

6 months (Figures 9, 10) of phenytoin therapy and serum folic acid levels assessed before the morning dose of phenytoin. Results were tabulated and subjected to statistical analysis.

Method of Statistical Analysis: The statistical analysis was done using t-test and the baseline serum folate levels and the serum folate levels obtained after 6 months of phenytoin therapy were correlated with the respective grades of gingival enlargement using Pearson's coefficient formula.

5. Results

The present study was designed in the Department of Oral Medicine and Radiology, Government Dental College and Research Institute, Bangalore during the period of Jan 2009 to Dec 2009 to assess the correlation between phenytoin induced gingival enlargement and serum folate levels. Selected epileptic patients to be enrolled in the study based on defined inclusion and exclusion criteria were explained in detail about the planned study and written informed consents were obtained.

The study consisted of a total of 25 patients with 19 male (76%) and 6 female (24%) patients. (Fig. 11), the mean age of the study group was 30.08 years with an age range of 18-50 years. The mean age of the 19 male patients included in the study was 30.26 years with an age range of 18-50 years while for the 6 female patients with an age range of 20-36 years, the mean age was calculated to be 29.5 year, (Fig. 12)

The study revealed a higher incidence of gingival enlargement in phenytoin treated epileptic patients with the observation of gingival enlargement in all patients in the test group after 6 months of phenytoin administration, though to varying grades.

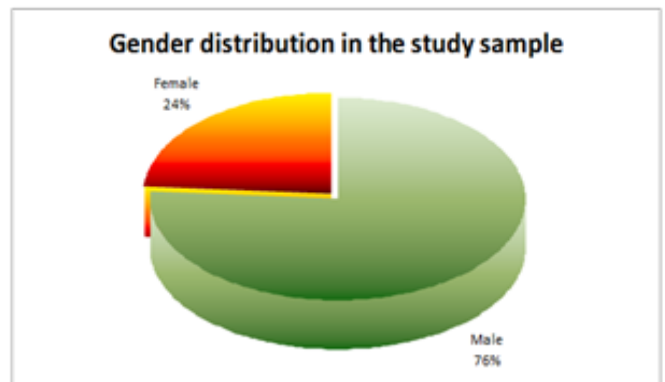


Figure 11. Pie diagram representing gender distribution in the study sample

The study also observed serum folic acid levels in selected epileptic patients prior to the start of and after 6 months of phenytoin therapy in addition to the age and sex matched controls. Assessment of serum folic acid level was done by chemiluminiscent method using Immulite kit.

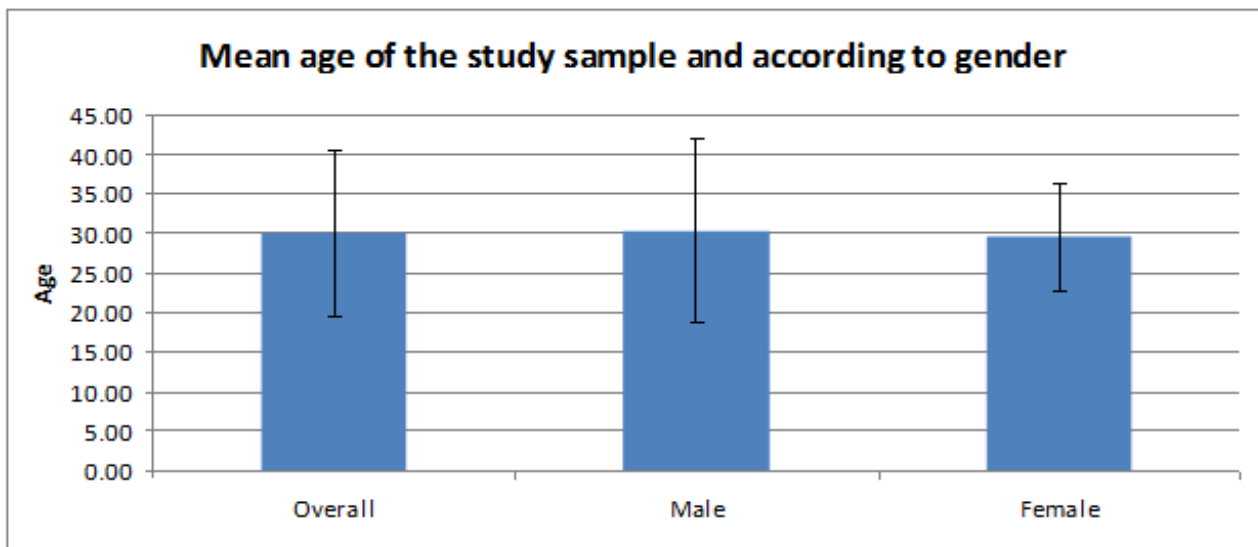


Figure 12. Bar diagram representing mean age in the study sample

Table 1. Depicting comparison of mean serum folate levels in the test and control groups before initiation of phenytoin treatment

Group	n	Mean	SD±	Mean difference	t	P-Value
Test Group	25	7.48	2.04	-6.982	-8.198	<0.001*
Control Group	10	14.46	2.81			

*denotes significant difference

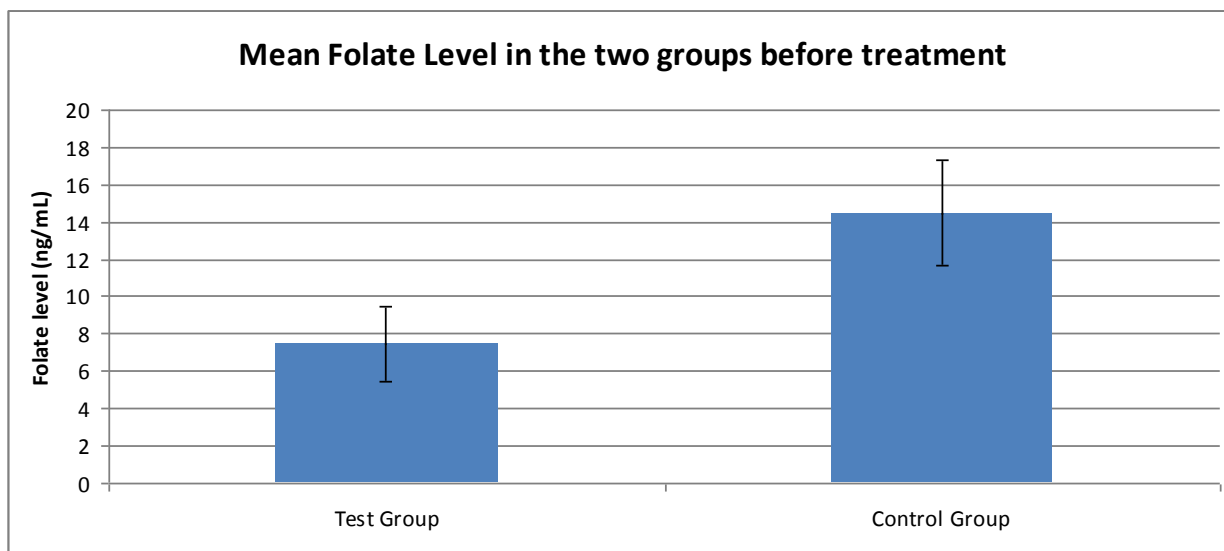


Figure 13. Bar diagram comparing mean serum folate levels in the test and control groups before initiation of phenytoin treatment

Table 2. Depicting mean serum folate levels with range in case of male and female patients before initiation of phenytoin treatment

Mean serum Folate Levels - Before	Mean	SD±	Median	Min	Max	Range
Male	7.16	2.19	6.5	3.87	10.9	7.03
Female	8.49	1.06	8.7	6.62	9.39	2.77

Table 3. Depicting overall mean grades for gingival enlargement with range, and same in case of male and female patients before initiation of phenytoin treatment

Gingival Enlargement-Before	Mean	SD±	Median	Min	Max	Range
Male	1.74	0.21	1.8	1.33	2.17	0.84
Female	1.58	0.26	1.5	1.33	2.08	0.75

Table 4. Depicting comparison of mean serum folate levels in the test and control groups after 6 months of phenytoin treatment

Group	n	Mean	SD±	Mean difference	t	P-Value
Test Group	25	3.90	1.95	-10.556	-12.714	<0.001*
Control Group	10	14.46	2.81			

*denotes significant difference

Table 5. Depicting mean serum folate levels with range in case of male and female patients after 6 months of phenytoin treatment

Mean serum Folate Levels - After	Mean	SD±	Median	Min	Max	Range
Male	3.63	2.01	2.7	2.02	8.71	6.69
Female	4.77	1.58	4.7	2.46	7.43	4.97

Table 6. Depicting overall mean grades for gingival enlargement with range, and same in case of male and female patients after 6 months of phenytoin treatment

Gingival Enlargement-After	Mean	SD±	Median	Min	Max	Range
Male	2.04	0.38	2.0	1.17	2.67	1.50
Female	2.14	0.23	2.2	1.83	2.42	0.59

Table 7. Depicting comparison of mean serum folate levels in the test group before and after 6 months of phenytoin treatment

Group	n	Mean	SD±	Mean difference	t	P-Value
Before treatment	25	7.48	2.04	3.574	10.242	<0.001*
After treatment	25	3.90	1.95			

*denotes significant difference

Table 8. Depicting comparison of mean grades for gingival enlargement in the test group before and after 6 months of phenytoin treatment

Group	n	Mean	SD±	Mean difference	t	P-Value
Before treatment	5	1.70	0.23	-0.365	-4.807	<0.001*
After treatment	5	2.07	0.35			

*denotes significant difference

Average serum folate level in our study was 7.48 +/- 2.04 ng/mL (Table 1/Fig. 13) prior to the start of phenytoin therapy with an average serum folate level of 7.16 +/- 2.19 ng/mL and a range of 3.87-10.9 ng/mL for the male and 8.49 +/- 1.06 ng/mL with a range of 6.62-9.39 ng/mL for the female patients. (Table 2) The average serum folate level for the age and sex matched 10 control

samples was found to be 14.46 +/- 2.81 ng /mL. (Table 1 and Fig. 13)

The gingival status was assessed using the index originally described by ANGELOPOULOS and GOAZ and later, modified by MILLER AND DAMM [GO INDEX] prior to the start of and after 6 months of phenytoin therapy.

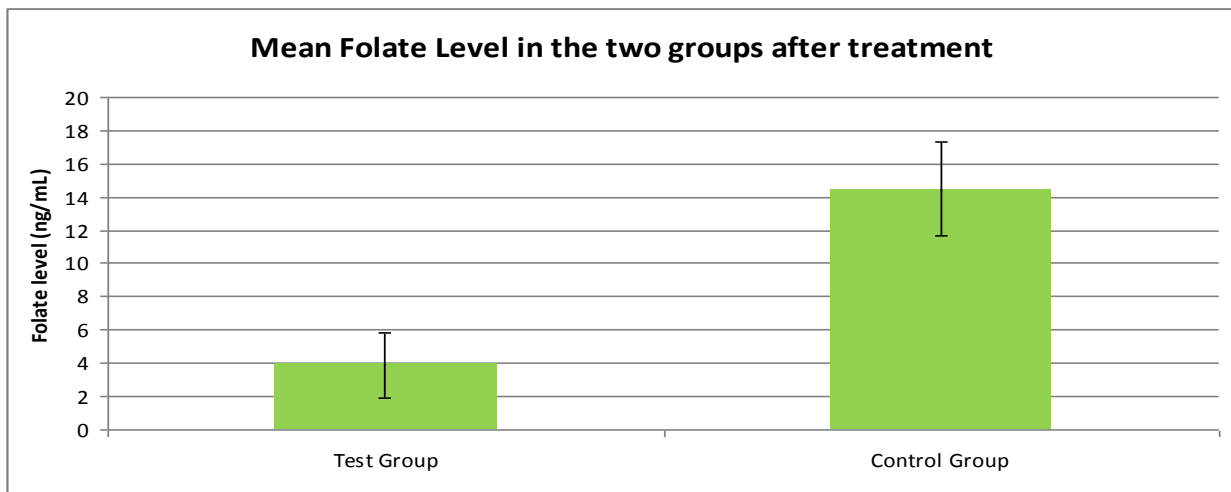


Figure 14. Bar diagram representing mean serum folate levels in the test and control groups after 6 months of phenytoin treatment

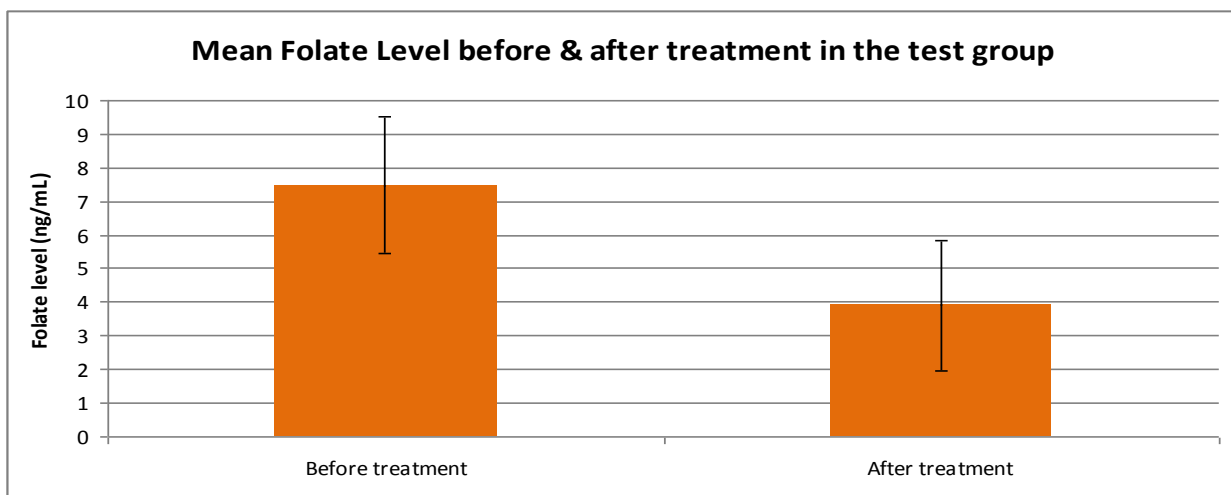


Figure 15. Bar diagram comparing mean serum folate levels in the test group before and after 6 months of phenytoin treatment

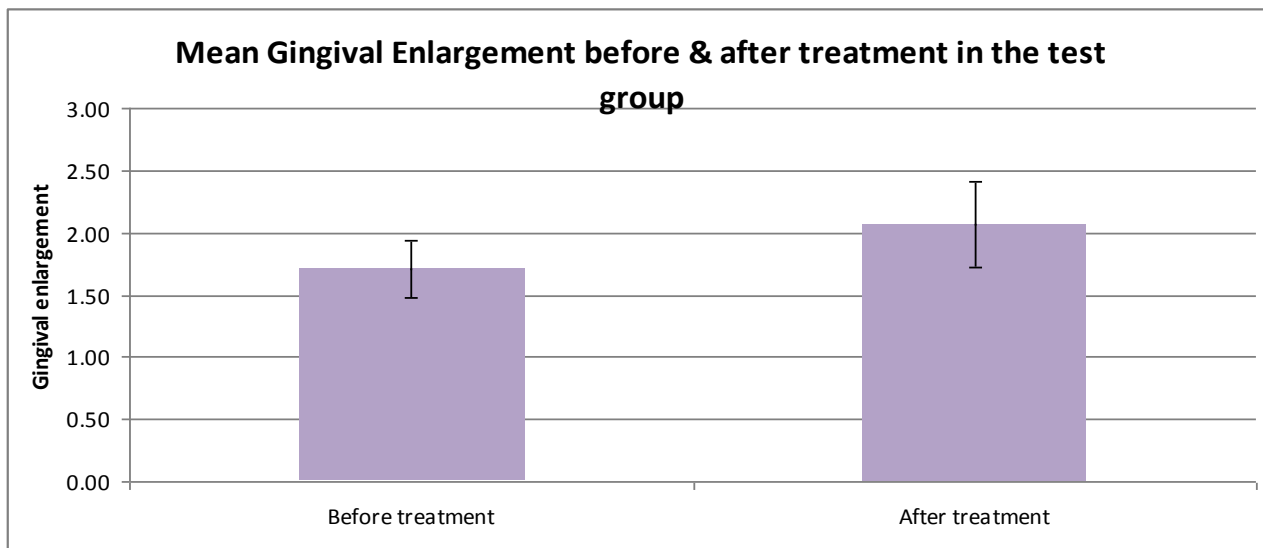


Figure 16. Bar diagram representing mean grades for gingival enlargement in the test group before and after 6 months of phenytoin treatment

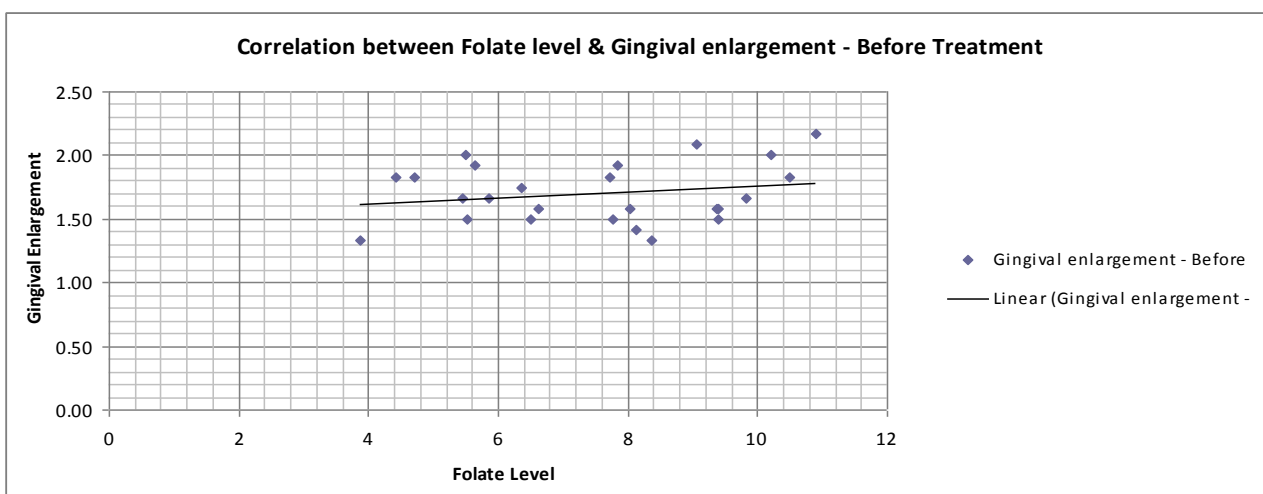


Figure 17. Scatter diagram comparing mean serum folate levels and grades for gingival enlargement before initiation of phenytoin treatment

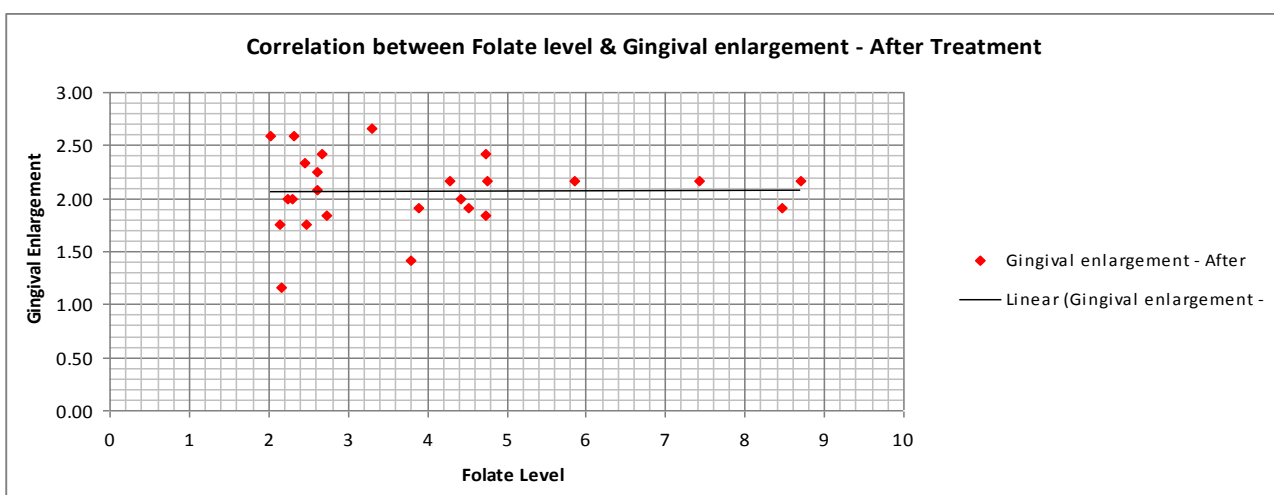


Figure 18. Scatter diagram comparing mean serum folate levels and grades for gingival enlargement after 6 months of phenytoin treatment

The average score of gingival enlargement prior to the start of phenytoin therapy in our study was found to be 1.74 +/- 0.23. In our study, an average grade of 1.74 +/- 0.21 was obtained for the gingival enlargement in the 19 male

patients included in the study with a range of 1.33-2.17 and 1.58 +/- 0.26 with a range of 1.33-2.08 for the 6 female patients. (Table 3) amongst these, 22 patients were found to have an approximate grade 2 while 3 patients

with grade 1 gingival enlargement.

After 6 months of phenytoin therapy, the average serum folate level in the study group was found to be 3.9 +/- 1.95 ng/mL (Table.4/Fig. 14) with an average 3.63 +/- 2.01 ng/mL for the male while 4.77 +/- 1.58 ng/mL for the female patients with a range of 2.02-8.71 ng/mL and 2.46-7.43 ng/mL respectively (Table5).

After 6 months of phenytoin therapy, the average grade for gingival enlargement was found to be 2.07 +/- 0.35. After 6 months of phenytoin treatment, average grade for gingival enlargement was found to be 2.04 +/- 0.38 with a range of 1.17-2.67 in the male patients while 2.14 +/- 0.23 with a range of 1.83-2.42 for the female patients. (Table 6), amongst these, 20 patients were found to have nearing grade 2, 2 patients, grade 1 and 3 patients, grade 3 gingival enlargement.

The statistical analysis was done using t-test and the baseline serum folate levels and the serum folate levels obtained after 6 months of phenytoin therapy (Fig. 15) were then correlated with the respective grades of gingival enlargement (Fig. 16) using Pearson's coefficient formula.

The results arrived found the reduction in mean serum folate levels before and after 6 months of phenytoin treatment to be statistically significant. (Table 7) The increase in mean gingival enlargement from before to after 6 months of phenytoin therapy was also found to be statistically significant. (Table 8) In either case, the p-value came out to be less than 0.001 with the level of significance kept at 0.05.

A positive correlation was also noted between the mean serum folate levels and the mean gingival enlargement before and after 6 months of phenytoin treatment. (Figs. 17 and 18)

6. Discussion

Despite tremendous advances in the management of epilepsy in the recent decade, the anti-epileptic drug phenytoin still remains the prime drug of choice in the management of epileptic patients in India [9, 10].

Chronic administration of phenytoin has been associated with a number of adverse effects [11, 12]. Gingival enlargement is one such most often reported adverse drug consequence of long term phenytoin usage [13].

In our study, 25 patients between the ages of 18-50 years visiting the Department of Neurology, Victoria Hospital, Bangalore during the period of Jan 2009 to Dec 2009 clinically diagnosed with epilepsy were selected prior to the start of phenytoin therapy based on the defined inclusion and exclusion criteria. The study consisted of a total of 19 male (76%) and 6 female (24%) patients. The mean age of the study group was 30.08 years with an age range of 18-50 years. The mean age of the 19 male patients included in the study was 30.26 years with an age range of 18-50 years while for the 6 female patients with an age range of 20-36 years, the mean age was calculated to be 29.5 years.

Numerous reports suggest that phenytoin induced gingival enlargement is more commonly seen in younger age groups. This is in concordance with the observations

of the several epidemiological studies conducted by Thomason et al, 1992, Steinberg and Steinberg, 1982, Dahllof and Modeer, 1986, and Stinnett et al, 1987. Also, both genders have been reported to be equally susceptible to phenytoin induced gingival enlargement in the literature [13]. The above mentioned observations were confirmed in our study as well since most of the patients with more severe gingival enlargements were in the age group of 20-40 years and the cases were reported with equal frequency in both the male and female patients.

The study revealed a high incidence of gingival enlargement in epileptic patients on phenytoin therapy with the observation of varying grades of gingival enlargement in all patients in test group after 6 months of phenytoin administration.

The incidence of phenytoin induced gingival enlargement as reported by a study conducted by Kimball was found to be 57% while other studies conducted in relation to incidence of phenytoin induced gingival enlargement have revealed wide incidence ranges of 20-40 % [14, 15] in some studies to 6-79 % in others [15]-[20], while 3-93% in few other studies [21, 22] and 50% in institutionalized epileptic patients (Seymour, 1993) as reported in the literature. The incidence of gingival overgrowth in the normal population has been reported to be between 4-7.5% [23]. This wide range of variability may be attributed to the small number of the cases reported in some publications to large variations in phenytoin dosages to variations in the length of phenytoin exposure and to differences in the age of the patients included in the various studies as well.

Drug induced gingival enlargement normally begins at the interdental papillae and is more frequently found in the anterior segments of the jaws though it often involves all the surfaces of teeth and is generalized in its distribution. [11, 19, 20]. Gradually, gingival lobulations are formed that may appear inflamed or more fibrotic in nature depending on the degree of local factors' induced secondary inflammatory changes.

All the clinical features of phenytoin induced gingival enlargement were confirmed in our study wherein we observed a predominantly firm and fibrotic nature of the gingival enlargement in most of the patients with local factors' induced secondary inflammatory changes having a minor role, if any, to play in the clinical picture of the phenytoin induced lesions of gingival enlargement as the oral hygiene was meticulously maintained. The observations of our study also revealed that the interdental papillae were the most common sites of involvement for the phenytoin induced gingival enlargements. The tissues affected were though not subjected to a detailed histo-pathological analysis as the patients were not subjected to surgical therapeutic options for the treatment that carries a high probability for recurrence [10, 11, 13].

Also, significant was the observation that the gingival enlargement induced by phenytoin was usually generalized with involvement of all surfaces of the teeth in all the quadrants but was more severe in the anterior segments of the jaws as per the observations of the prior studies possibly because of a relative lack of oral hygiene

maintenance in these areas of the jaws.

A review of the gingival enlargement indices proposed in the literature clearly demonstrates their diversity, from the most simple gingival enlargement index proposed to the most elaborate one. Different authors have used different criteria for grading the gingival enlargement in their studies however there is no universal criteria that can be adopted for the same as every criteria has a more or less subjective methodological approach for the assessment of gingival enlargement and depends on the author's discretion for following the same. The majority of the indices used to quantify gingival enlargement are difficult to reproduce because they lack an objective criteria to differentiate between the degree of horizontal and vertical overgrowth.

In our study, the gingival status was assessed using the index originally described by ANGELOPOULOS and GOAZ and later, modified by MILLER AND DAMM [GO INDEX]. The height of gingival tissue was measured from the cemento-enamel junction to the free gingival margin. The grades for gingival enlargement were assessed in relation to the six anterior teeth in both the maxillary and mandibular arches. The enlargement was recorded both on the mesial and the distal inter-proximal aspects and the greater score amongst them was selected to be included to refer to the peak effect of the drug. Other criteria for assessing the gingival enlargement were not followed for their being with too extensive methodologies and yet with highly subjective nature of assessment of gingival enlargements.

In our study, an average grade of 1.74 +/- 0.21 while 1.58 +/- 0.26 was observed for the gingival enlargement in the 19 male and 6 female patients respectively. Amongst these, 22 patients were found to have an approximate grade 2 while 3 patients with grade 1 gingival enlargement.

After 6 months of phenytoin treatment, average grade for gingival enlargement was found to be 2.04 +/- 0.38 in the male while 2.14 +/- 0.23 for the female patients. Amongst these, 20 patients were found to have nearing grade 2 and 3 patients, grade 3 gingival enlargement.

The results obtained could not be compared with the observations of other studies as the indices followed were either different, modified Harris and Ewalt index in a study conducted by Prasad V N et al on the role of folic acid in the prevention of phenytoin induced gingival enlargement on sixty epileptic children in the age range of 8-13 years [8] or even using the same index in a cross sectional study conducted by L Brunet et al on 59 patients on anti-epileptic medications using the GO and MB indices [13] owing to the subjectivity of the assessment procedure and a lack of reproducibility with local factors further playing a confounding role in the observations.

In our study, assessment of serum folic acid was done by chemiluminiscent method using Immulite kit prior to the start and after 6 months of phenytoin therapy. Other methods used to assess serum folates that have been described in the literature include the one of immunoassay method and the less reliable and a relatively less sensitive assay of serum folate levels using *Lactobacillus casei* as the test organism. Average range of serum folate levels in

normal controls as standardized by few studies has been found to be 3-17 ng/mL.

Serum folate levels were earlier quantified by means of a radioimmunoassay method using a SimulTRAC Radioassay kit in a study conducted by Majola M P et al [24] involving a total of 134 patients on the factors influencing phenytoin-induced gingival enlargement. The average serum folate levels in the study ranged from 1.2 ng/mL to 14.7 ng/mL with a mean value of 4.6 ng/mL.

The mean serum folate level as assayed with the help of *Lactobacillus casei* method was found to be 4.76 ng/mL in the normal controls and 3.96 ng/mL in the epileptic patients in the study conducted by E. H. Reynolds et al [25] involving 33 normal controls, 34 epileptic outpatients, 19 of whom also suffered from psychiatric illness, 33 epileptic inpatients with psychiatric illness and 30 non-epileptic inpatients with psychiatric illness on folate metabolism in epileptic and psychiatric patients.

Serum folate levels were on the other hand found to be 8.8 +/- 3.6 ng/mL with a range of 2.9-16.1 ng/mL in controls while 4.1 +/- 1.6 ng/mL with a range of 1.2-6.7 ng/mL in 16 amongst a total of 75 epileptic patients on phenytoin therapy in the study conducted by Ufuk Sener et al [26] on the effects of common anti-epileptic drug monotherapy on serum levels of homocysteine, vitamin B12, folic acid and vitamin B6. Serum folate levels in this study were measured by the immunoassay method using commercial kit, Immulite, DPC, United States. Normal range of serum folates in healthy adults as estimated by *Lactobacillus casei* method has been standardized to be 2.5-15 ng/mL.

Average serum folate level was 7.48 +/- 2.04 ng/mL prior to the start of phenytoin therapy with an average serum folate level of 7.16 +/- 2.19 ng/mL and a range of 3.87-10.9 ng/mL for the male and 8.49 +/- 1.06 ng/mL with a range of 6.62-9.39 ng/mL for the female patients in our study. The average serum folate level for the age and sex matched 10 control samples was found to be 14.46 +/- 2.81 ng/mL.

The baseline serum folate levels were later compared with the levels obtained after 6 months of phenytoin therapy and simultaneously were correlated with the average grades obtained for gingival enlargement.

After 6 months of phenytoin therapy, the average serum folate level in the study group was found to be 3.9 +/- 1.95 ng/mL with an average 3.63 +/- 2.01 ng/mL for the male while 4.77 +/- 1.58 ng/mL for the female patients with a range of 2.02-8.71 ng/mL and 2.46-7.43 ng/mL respectively.

The wide variations found in the mean and average range of serum folate levels in different age groups and genders from the previous studies likely reflected the differences among the study samples in terms of age and health status as well as differences in the assessment procedures.

This is a preliminary study; the results of the study suggest a higher incidence and severity of gingival enlargement in phenytoin treated epileptic patients with a positive correlation between serum folic acid levels and gingival enlargement before and after 6 months of phenytoin administration. No available published reports

with similar methodology have been found in the literature. Hence, this study gives a scope for further studies with larger sample size and estimation of tissue level folates to conclude the results.

7. Conclusion

This is a preliminary study which aims at the assessment of serum folate levels in epileptic patients who are on long term phenytoin therapy and their association with phenytoin induced gingival enlargement. The statistical analysis of the results suggests, a high incidence and increased severity of gingival enlargement in epileptic patients on phenytoin therapy. A positive correlation between gingival enlargement and average serum folate levels before and after phenytoin administration and significant drop in serum folate levels after 6 months of phenytoin treatment.

Since this is only a baseline study, the results of the study encourage for further studies with larger sample size and estimation of tissue level folates to conclude the results.

Acknowledgment

We thank all the people who directly and indirectly contributed for the study as the study required intense efforts from the people outside our Department including Department of Neurology and Department of Clinical Biochemistry, Bangalore Medical College and Research Institute and Associated Hospitals.

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