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Original Article

# A study on gingival enlargement and folic acid levels in phenytoin-treated epileptic patients: Testing hypotheses

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## Abstract

**Background:** There have been studies that report clinical benefits of the use of folic acid as an adjuvant to the antiepileptic therapy in the prevention of antiepileptic drug-induced gingival enlargement. However, studies 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. 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. 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.

**Methods:** A total of 25 patients aged between 18 and 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.

**Results:** The results of the study confirmed a significant association between low serum folate levels with increasing severity as well as an early onset of phenytoin-induced gingival enlargement.

**Conclusions:** 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.

**Key Words:** Epilepsy, gingival enlargement, folic acid, phenytoin

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## INTRODUCTION

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 a frequently reported adverse effect of phenytoin.[8,15] Approximately 40-50% of the patients treated with phenytoin develop esthetically disfiguring enlargement of the gingivae. Whenever this occurs, 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 pseudo-pockets that are formed as a result of gingival enlargement increase plaque retentive areas that further predispose the patient toward an enhanced susceptibility for inflammatory changes in the gingivae, dental caries, and periodontal diseases.[7,31]

The etio-pathogenesis of phenytoin-induced gingival enlargement is still not clearly understood, however, many studies indicate its multi-factorial etiology[1,2] 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 especially, absorption thereby leading to a significant decrease in the plasma as well as the tissue levels of folates.[29]

Folates administered at pharmacological doses, in contrast, though have been seen to lead to a substantial decrease in the incidence of gingival hyperplasia,[3] have been blamed for a significant decrease in the serum concentration of phenytoin severe enough to precipitate seizures.[5,10,24] The use of folates as an adjuvant to the antiepileptic therapy in the prevention of gingival enlargement, therefore, 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.[23] More recently, Arya *et al*. demonstrated that oral supplementation in children can decrease the incidence of gingival hyperplasia.[3] There has been consistent void, however, 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. The objectives of the study were to study the incidence and assess the scores of gingival enlargement in epileptic patients before and after 6 months of phenytoin therapy; to assess serum folic acid levels before and after 6 months of phenytoin therapy and to correlate the scores of gingival enlargement with serum folic acid levels in patients on phenytoin therapy.

## MATERIALS AND METHODS

### Source of data

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

### Method of collection of data

Selected epileptic patients in the age group of 18-50 years, who were clinically diagnosed with epilepsy and being started with phenytoin therapy and who were with full complement of teeth without any carious or periodontal involvement or any other pathological process in the teeth and the jaws, were explained in detail about the planned study and written informed consents were obtained. The patients were exclusively being started on phenytoin therapy and were not supposed to take any other medication apart from phenytoin throughout the course of the study. The patients who required polytherapy with other drugs in combination with phenytoin were excluded from the study. These patients were subjected to a detailed history and a thorough clinical examination using a specially prepared proforma.

Epileptic patients with other systemic diseases; with preexisting gingival enlargements due to any reasons as idiopathic, inflammatory, neoplastic, endocrinal, chronic vitamin C deficiency, mouth breathing or pregnancy; epileptic patients on any type of pharmacologic therapy including multi-vitamins or folate antagonists; and who had history of dental treatment and trauma to teeth were excluded from the study.

## 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.

### Assessment of serum folic acid

Assessment of serum folic acid level was done by chemiluminiscent method using Immulite kit prior to the start of phenytoin therapy. A minimum gap of 10 hours after the last meal followed by intake of drug was considered as the standard fasting period in the patients. 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 by ultracentrifugation. The supernatant was discarded and the rest of the sample was stored at −20°C. The Flurometer was set at 370 nm excitation with emission monitored at 470 nm. Flow rate was adjusted as 1.3 ml/min.

Controls were assessed only once based on their inclusion according to age and sex. They were free of any systemic disease process and were not on any drugs including supplementation with synthetic vitamin supplements or the drugs, which could have interfered with the absorption of such nutrients.

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 [GO INDEX][1,2,8] [Figure 1].

## Assessment of gingival enlargement

The gingival status was assessed using the [GO INDEX].[1,2,8] There were a total of four investigators who assessed gingival enlargements and were blinded to the purpose of the study as well as blinded to the sera levels of folic acid. 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 among 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 reassessed [Figure 2] using the same criteria. The same procedure was repeated at the end of 6 months [Figures 3 and 4] of phenytoin therapy and serum folic acid levels assessed before the morning dose of phenytoin. Results were tabulated and subjected to statistically 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.

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

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

**Figure 3: Clinical picture of gingival enlargement in a male epileptic patient (GRADE 2) after 6 months of phenytoin therapy**

**Figure 4: 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**

## 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 January-December 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. 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.

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.

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.

Average serum folate level in our study was 7.48 ± 3.91 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. 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 gingival status was assessed using the index originally described by Angelopoulos and Goaz and later modified by Miller and Damm Gingival Overgrowth Index (GO Index) prior to the start of and after 6 months of phenytoin therapy.

The average score of gingival enlargement prior to the start of phenytoin therapy in this study was found to be 1.7 ± 0.23. In this 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. Among 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 ± 5.31 ng/mL with an average 3.63 ± 2.01 ng/mL for male patients 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.

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. Among 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 were then correlated with the respective grades of gingival enlargement 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 1]. The increase in mean gingival enlargement from before to after 6 months of phenytoin therapy was also found to be statistically significant [Table 2]. In either case, the *P* value was 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 [Figures 5 and 6].

## DISCUSSION

Despite tremendous advances in the management of epilepsy in the recent decade, the antiepileptic drug phenytoin still remains the prime drug of choice in the

**Table 1: Depicting comparison of mean serum folate levels in the test group before and after 6 months of phenytoin treatment**

| Group | *n* | Mean | Std dev | Mean difference | *t* | *P* value |
|---|---|---|---|---|---|---|
| Before treatment | 25 | 7.48 | 3.91 | 3.574 | 10.242 | <0.001* |
| After treatment | 25 | 3.9 | 5.31 | | | |

*denotes significant difference

**Table 2: Table depicting comparison of mean grades for gingival enlargement in the test group before and after 6 months of phenytoin treatment**

| Group | *n* | Mean | Std dev | Mean difference | *t* | *P* value |
|---|---|---|---|---|---|---|
| Before treatment | 25 | 1.70 | 0.23 | −0.365 | −4.807 | <0.001* |
| After treatment | 25 | 2.07 | 0.35 | | | |

*denotes significant difference

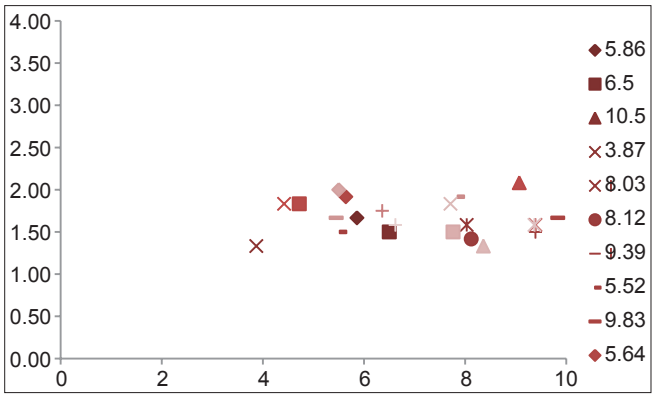


**Figure 5: Scatter diagram comparing mean serum folate levels and grades for gingival enlargement before initiation of phenytoin treatment. Along X-axis - Mean serum folate levels in ng/mL, Along Y-axis - Grades for gingival enlargement**

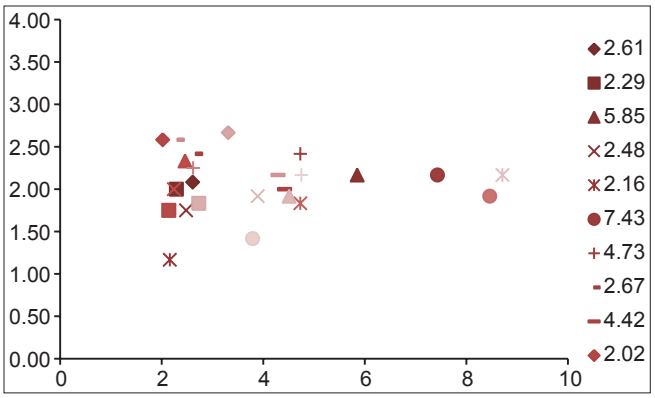


**Figure 6: Scatter diagram comparing mean serum folate levels and grades for gingival enlargement after 6 months of phenytoin treatment. Along X-axis - Mean serum folate levels in ng/mL, Along Y-axis - Grades for gingival enlargement**

management of epileptic patients in India.[17,27]

Chronic administration of phenytoin has been associated with a number of adverse effects.[11,16] Phenytoin-induced gingival overgrowth is one such most frequently reported gingival lesion, which was first described in 1939.[8,15]

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. In addition, both genders have been reported to be equally susceptible to phenytoin-induced gingival enlargement in the literature.[8] The above mentioned observations were confirmed in our study as well.

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 by Kimball was found to be 57% while other studies in relation to incidence of phenytoin-induced gingival enlargement have revealed wide incidence range of 20-40%[9,30] in some studies to 6-79% in others[4,13,14,21,26,30] while 3-93% in few other studies[18,19] 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% and 7.5%.[32] 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.[14,16,21] 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 this 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.[8,16,17]

In addition, 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 this study, the gingival status was assessed using the index originally described by Angelopoulous and Goaz[1,2] and later modified by Miller and Damm [GO INDEX].[8] 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.

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 by Prasad *et al.* on the role of folic acid in the prevention of phenytoin-induced gingival enlargement on 60 epileptic children in the age range of 8-13 years;[23] or even using the same index in a cross sectional study by Brunet *et al.* on 59 patients on antiepileptic medications using the GO and MB indices[8] 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 by Majola *et al.*[20] 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 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 by Reynolds *et al.*[25] involving 33 normal controls, 34 epileptic out-patients, 19 of whom also suffered from psychiatric illness, 33 epileptic in-patients with psychiatric illness, and 30 nonepileptic in-patients with psychiatric illness on folate metabolism in epileptic and psychiatric patients.

Serum folate levels were, in contrast, 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 among a total of 75 epileptic patients on phenytoin therapy in the study by Sener *et al.*[28] on the effects of common antiepileptic drug mono-therapy 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.

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.

In addition, numerous studies in the past suggest the possible role of folic acid in the prevention of phenytoin-induced gingival enlargement as well as its recurrence following a surgical removal.[6,12,22] In the study by Arya *et al.*, 120 pediatric patients that developed gingival hyperplasia due to phenytoin use were included and followed-up for 6 months. During the study, 62 patients were treated with folic acid against 58 patients who were kept on placebo. Gingival hyperplasia was found to be significantly reduced in patients treated with folic acid. However, a limitation of the study was that folate levels were not measured in either the control or treatment groups.[3] To add, the results of most of the studies indicate that topical folates lead to a significantly inhibited gingival hyperplasia than either systemic folate or placebo group.[12] A recent study, however, has also concluded that systemic folic acid prescribed along with phenytoin reduces the incidence and delays the onset and severity of phenytoin-induced gingival enlargement.[23]

This is, however, 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.

## 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:

1. A high incidence and increased severity of gingival enlargement in epileptic patients on phenytoin therapy
2. A positive correlation between gingival enlargement and average serum folate levels before and after phenytoin administration; and
3. A significant drop in serum folate levels after 6 months of phenytoin treatment.

Thus, the use of folic acid as an adjuvant to phenytoin therapy in the prevention of phenytoin-induced gingival enlargement calls for further studies in future keeping in mind the precipitation of epileptic attacks seen in a significant number of patients on folic acid adjuvant therapy secondary to fall in the sera levels of phenytoin due to the propensity of drug interactions between the two. 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.

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