Phenytoin and Gingival Enlargement: A Brief Overview of Etio-Pathogenesis

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ABSTRACT

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. 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. 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. However, the etio-pathogenesis of phenytoin induced gingival enlargement is still not clearly understood, although, a number of studies indicate its multi-factorial etiology including oral hygiene status of the affected epileptic patients. The present review gives an overview regarding the association of phenytoin and gingival enlargement seen in epileptic patients being treated with the drug, excluding the role of local factors, if any, with the maintenance of a meticulous oral hygiene.

Key words: Epilepsy; gingival enlargement; phenytoin.

INTRODUCTION

Gingival enlargement has been described as one of the most frequent adverse effects associated with long term phenytoin therapy. Drug-induced gingival enlargement (DIGE) associated with chronic use of the anti-epileptic drug phenytoin was first reported in 1939 by Kimball. In the same year, Faurbye and in 1959, Strean &
Leoni (3) suggested that the alkalinity of phenytoin might be the cause of the gingival side effect. In 1948, Brandon (4) hypothesized that phenytoin had a direct action on the gingival tissues. In 1975, Angelopoulos (5) argued that phenytoin induced degranulation of mast cells which resulted in the generation of a substance that increased collagen formation. Larmas, (6) in 1976, suggested that phenytoin had a proliferating effect primarily on the basal cell layer of the oral epithelium thus increasing the epithelium-connective tissue interface area, which was confirmed by Hassel et al. (7) Furthermore, the oral epithelium may have an inducing effect on the underlying fibroblasts, in which specifically alkaline phosphatase may be involved. In 1977, Vogel (5) speculated that phenytoin induced gingival enlargement was due to an end-organ folic acid deficiency, which could lead the gingival tissues susceptible to inflammation by causing degenerative changes in the gingival sulcular epithelium, the main physical barrier against local irritants. Apart from elevated production of connective tissue matrix in the phenytoin induced gingival enlargements, in-vitro research has also focused on the possibility of an accumulation of redundant tissue as a result of inhibition of matrix breakdown. While cells from phenytoin induced gingival enlargements have been seen to synthesize and secrete elevated quantities of collagenase, the majority of the enzyme produced by such cells has been found to be inactive. Also, Narayanan and Hassell (7) had characterized the collagen types present in normal gingival tissues and in phenytoin induced gingival enlargements and detected that the latter manifested less of type I and more of type III collagen. Furthermore, it has been demonstrated in vitro that phenytoin directly inhibits the conversion of inactive collagenase pro-enzyme to the active form. Ultrastructurally, the fibroblasts of phenytoin induced gingival enlargements exhibit a decrease in the volume density of rough endoplasmic reticulum and a smaller nuclear to cytoplasmic ratio with possible implication of this being that while the fibroblasts of the phenytoin treated gingival enlargements are synthetically active, they are possibly less active in degradative functions thus accounting for the alterations in the gingival connective tissue matrix. (8) This review gives an overview regarding the association of phenytoin and gingival enlargement seen in epileptic patients being treated with phenytoin.

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. (8, 11) Gingival enlargement is one such most often reported adverse drug consequence of long term phenytoin usage. (12)

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. (12) 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 % (13, 14) in some studies to 6-79 % in others (14-19) while 3-93% in few other studies (20, 21) 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%. (22) 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.

Phenytoin 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. (8, 18, 19) 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. The patients although are not subjected to surgical therapeutic options for the treatment that carries a high probability for recurrence. (8, 10, 12)

Numerous studies conducted in the past have proposed a plethora of the possible etiologies for the same. This review focuses on the more common etiologies proposed behind phenytoin induced gingival enlargement which have received widespread acceptance.

Drug-Induced Gingival Enlargement: Drug-induced enlargement has been associated with a patient's genetic predisposition. (8) Some investigators assert that underlying inflammation is necessary for the development of drug-induced enlargement, (11) while others purport that the existing enlargement induced by the drug effect compounds plaque retention, thus furthering the tissue response. (23)

Gingival enlargement is associated with multiple factors including inflammatory (acute and chronic), idiopathic, drug-induced, neoplasia (benign and malignant tumors), hormonal disturbances, ascorbic acid (vitamin C) deficiency and with dental eruption. After that, gingival hypertrophy related to phenytoin, has been described as one of the drug induced gingival enlargement. (12)

Currently, more than 15 drugs have been identified as possible causative agents, including oral contraceptives. (16, 24) However, there are 3 classes of drugs that are well-established causes of gingival enlargement, being responsible for most cases: anti-epileptic agents, anti-hypertensive calcium antagonists and immunosuppressant cyclosporine. One property that is common to these 3 classes of drugs is that they all directly affect cellular calcium metabolism. Since cellular production of collagenase is modulated by calcium influx, fibroblasts from patients treated with these drugs may produce an inactive form of collagenase, being responsible for an increase in extra-cellular matrix. (12)

The precise mechanism by which drug-induced gingival enlargement occurs is still not completely understood, although a number of hypotheses have been suggested. (5) Phenytoin probably interacts with a subtype of susceptible fibroblasts, cyclosporine affects the metabolism of these cells and nifedipine enhances this effect reducing their metabolism. (10, 25) Several factors may influence the relationship between the various implicated drugs and components of the gingival tissues, including: age, genetic predisposition, pharmacokinetic variables, drug-induced alterations in gingival connective tissue homeostasis, ultra structural factors and
inflammatory changes, drug-induced action on growth factors, etc. Three significant factors which are considered to be the most important etiological factors in the expression of these gingival changes include: drug variables, plaque-induced inflammatory changes in the gingival tissues and genetic factors – the latter determining the heterogeneity of the gingival fibroblasts.

Also, some drugs induce a direct effect on a subgroup of fibroblasts, named “responders”, that are apparently genetically determined to be sensitive to the drug causing gingival growth. Such drugs produce a decrease in calcium influx (due to alterations in calcium-sodium exchange), which causes a decrease in cellular folic acid uptake (producing a localized folate deficiency) thus, limiting the production of the collagenase-activating enzyme (the active form of collagenase). Also, since the presence of inflammation secondary to dental plaque causes proliferative increases in connective tissue, the catabolic ability of collagenase is saturated, and the inhibited degradation of the extra cellular matrix causes a local accumulation of this matrix. However, several other factors may be involved in drug induced gingival enlargement including the so-named androgenic hormones.

Brown et al. (1991) have pointed out in this entity several factors: increase of sulphatid glicosamines, immunoglobulins, epithelial growth factor; calcium and sodium rupture efflux in fibroblasts, folic acid and collagenase deficiency. Saito et al. (1996) have shown by immunohistochemistry studies in gingival enlargement caused by phenytoin and nifedipine that the increase in beta-growing factor, basic growing fibroblast factor, its receptors and glicosaminoglicans heparan sulphate are involved; this was confirmed in other studies.

The clinical presentation of gingival hypertrophic and inflamed tissues is associated with specific macrophagic phenotypic picture that express betacitocine IL-1 in tissues or platelet derived growth factor. Iacopino et al. (1997) and Saito et al. (1999) have speculated that p53 protein expression in drug induced gingival enlargement suggests that its pathogenesis is involved with DNA abnormalities. Reduction of IgA salivary levels has also been accounted for the cause of gingival enlargement induced by phenytoin but it was not confirmed, as well as alteration of subgingival microflora.

Dose-dependent correlations with the severity of gingival overgrowth are weak, but decreased drug use in general results in reduced severity of gingival pathology. For example, phenytoin was reported to effuse into crevicular fluid without any correlation to the incidence of overgrowth (McLaughlin et al., 1995), while no direct link was shown between overgrowth and the concentrations of phenytoin and metabolites (Ball et al., 1996). A more recent study supports a correlation between diminished metabolism of phenytoin in affected individuals and overgrowth (Kamali et al., 1999), but this has not been confirmed.

Age, gender, concomitant medication with multiple drugs, local factors such as plaque accumulation, and genetic disposition are additional complicating risk factors in drug-induced gingival overgrowth (Thomason et al., 1995, 1996; Cebeci et al., 1996).

Treatment of the gingival overgrowth lesion itself can be complicated due to the superimposed inflammation on the fibrotic tissue enlargement. Traditionally, periodontal therapy offers removal of the inflammatory component of the overgrowth through scaling and gingival curettage, followed by excision of the overgrown gingiva (Kimball, 1939; Hassell...
and Hefti, 1991). For patients with severe gingival overgrowth and who require continuous drug therapy for medical reasons, gingivectomy must be repeated periodically due to the recurrent nature of drug-induced gingival overgrowth (Hall, 1997; Ilgenli et al., 1999; Kantarci et al., 1999).

In drug-induced gingival enlargements, reversing and preventing gingival enlargement is as easy as ceasing drug therapy. However, this is not always feasible; in such a situation, alternative drug therapy may be employed, if possible, to avoid this deleterious side effect. In the case of immuno-suppression, tacrolimus is an available alternative which results in much less severe gingival overgrowth than cyclosporin, but is similarly nephrotoxic. The dihydropyridine derivative isradipidine can replace nifedipine for some uses of calcium channel blocking and does not induce gingival overgrowth.

CONCLUSION

The results of the studies conducted in the past suggest a higher incidence and severity of gingival enlargement in phenytoin treated epileptic patients with local factors having a little role, if any, towards phenytoin induced gingival enlargement. The present review brings forth the possible etiologies behind the association of phenytoin and phenytoin induced gingival enlargement in epileptic patients being treated with phenytoin. However, further research is required to analyze the exact etiology behind these types of drug-induced gingival enlargements possibly by subjecting the tissues affected with a detailed histo-pathological analysis as the patients usually are not subjected to surgical therapeutic options for the treatment that carries a high probability for recurrence.

The review encourages for further studies to confirm the nature of histology of phenytoin induced gingival enlargement in phenytoin treated epileptic patients to find out the most feasible therapeutic options to overcome this inadvertent adverse sequel of long term phenytoin administration required for the management of patients suffering from this chronic disease.

Contributions from the author: Literature search, manuscript preparation, manuscript editing and manuscript review.

Ethical Declaration: The study has been approved by the ethical committee appointed by the Government Dental College and Research Institute, Bangalore and Bangalore Medical College and Research Institute, Bangalore and has therefore been performed in accordance with the ethical standards laid down in the 1975 declaration of Helsinki and its later amendments in 2000 after a written informed consent from the patients for their inclusion in the study. Details that might disclose the identity of the patient have been omitted.

Competing interests and other declarations: None

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